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SELENIUM BASED METHODOLOGY IN ORGANIC SYNTHESIS

by

CHARLES G. RUSSELL

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND

RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled SELENIUM BASED METHODOLOGY IN ORGANIC SYNTHESIS submitted by Charles G. Russell in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

D. L. J. Clive
Supervisor

Joseph Takats

E. E. Hogan

External Examiner

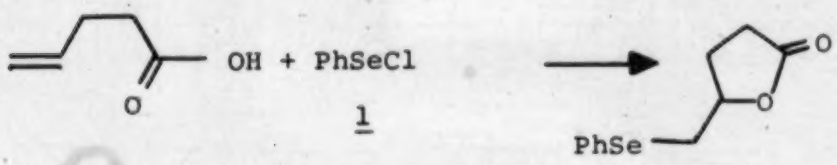
Date: August 26, 1981

TO MY WIFE MARLENE

Abstract

This thesis describes the following original contributions to the literature:

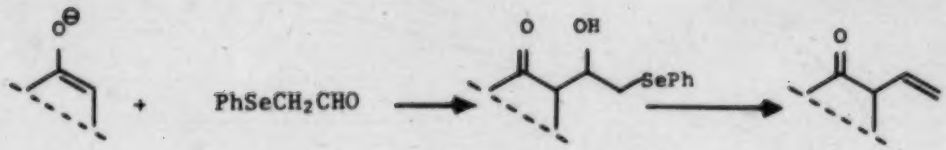
A) Benzeneselenenyl chloride 1 was found to react with unsaturated acids in a reaction of general application to give lactones (eq. (1)) in excellent yields. Mechanistic



(1)

details of this type of cyclization were examined and some of the aspects were elucidated. Evidence is given for the intervention of several intermediates in the reaction before formation of the final product and for some cases these intermediates are identified.

B) Phenylselenoacetaldehyde (2) was found to serve as a useful synthetic equivalent of a vinyl cation. It was discovered that the aldehyde undergoes aldol condensations in an efficient manner to afford the corresponding ketohydroxyselenide 3 which can then be converted to the α-vinylketone 4 (eq. (2)). Substrates such as 4 are excellent precursors for Cope and oxy-Cope rearrangements, processes which result in ring expansion to medium or large ring ketones. Preliminary results, using a recent



(2)

2 3 4

modification of the oxy-Cope rearrangement, indicate that the process depicted in equation (2) can be developed to the level of a repetitive ring expansion method, yielding macrocycles.

Acknowledgements

I would like to express my strong gratitude to Dr. D.L.J. Clive for his guidance during the course of my studies. I would also like to thank my wife Marlene for her continuous support and encouragement.

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Finally, I would like to thank Jacki Jorgensen for her meticulous typing of this thesis.

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INTRODUCTION

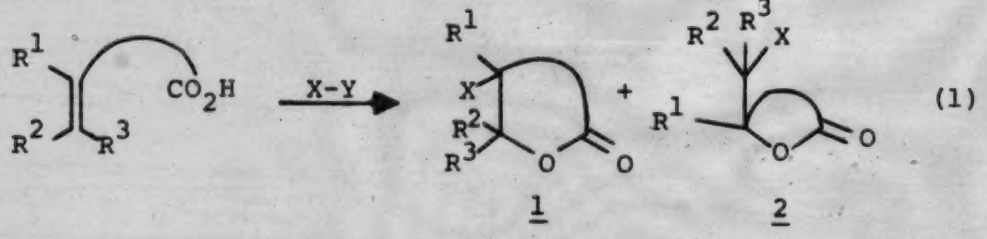
Organic synthesis requires, by its nature, a readily available battery of synthetic operations capable of effecting specific chemical transformations such that available substrates can be transformed via a number of reactions into structurally related but less available products. In order to carry out these transformations in an efficient manner it is desirable that the reagents used for the synthetic reactions operate under mild conditions and display functional, regiochemical and stereochemical selectivity. In the quest for such reagents a number of elements in the periodic table have been studied and their usefulness as synthetic reagents evaluated. One such element which has undergone rapid development as an organic reagent and has recently been reviewed[1] is selenium. Although selenium was first discovered in the early 1800's, more than a century passed before any of its chemistry was seriously examined.[2] Catalyzed, in part, by the extensive and invaluable development of organosulfur chemistry during the last two decades, the exploration of organoselenium chemistry is currently under rigorous and intensive investigation.

The topics within this thesis represent a further refinement and expansion of organoselenium-based methodology. Since two themes are dealt with, the thesis

is divided into two sections. In the first section, the use of phenylselenenyl chloride to lactonize unsaturated acids is examined in detail and some of the mechanistic aspects of the reaction are discussed. In the second section the use of phenylselenoacetaldehyde as a vinyl cation equivalent is described. The use of this synthon for ring expansion processes is examined and preliminary results on the use of the equivalent in repetitive ring expansions are given.

LACTONIZATION

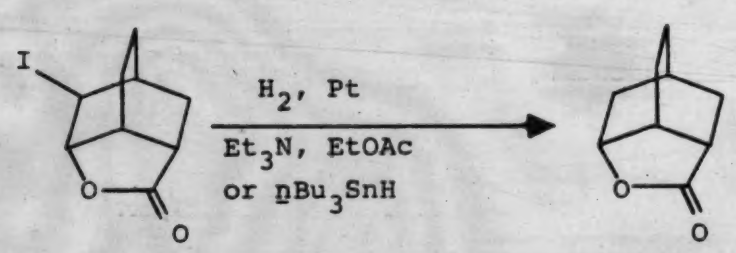
Lactones are an important class of compounds because of their widespread occurrence in nature and their potential as antitumor agents. Some of the more important types are the α-methylene lactones,[3] the unsaturated lactones (e.g., butenolides),[4] and macrolides.[5] Procedures for the construction of such lactones are both diversified and numerous. A method which has proven itself repeatedly throughout the literature for the construction of lactones is that involving the cyclization of unsaturated acids. Using this method an unsaturated acid is treated with a suitable electrophile (X) resulting in closure to the corresponding lactone (eq. (1)). In principle, two different product lactones (1 and 2) are possible. Common electrophilic reagents used to effect lactonizations



(1)

of this type are: lead tetraacetate,[6] mercury acetate,[7] acid[8] and halogen;[9] of these reagents, by far the most widely used is the halogen. Termed halolactonization, the reaction using a halogen as an electrophile has been

carried out most often with iodine and has been the subject of a recent review.[9] Generally, the reaction is performed by dissolving the unsaturated acid in aqueous sodium hydrogen carbonate and treating the resulting solution with potassium iodide and iodine. Once formed, the iodolactone usually separates out of solution. In practice, lactonization of β,γ or γ,δ unsaturated acids usually yields γ-iodolactones while δ,ε unsaturated acids yield δ-iodolactones. The corresponding dehalogenated lactone can be obtained from the iodolactone by either hydrogenolysis or hydride reduction (eq. (2)). In addition, an unsaturated lactone can be obtained from the iodolactone by treating it with a base such as DBN or DBU (eq. (3)). The unsaturated lactone formed is that which results by removal of the most acidic hydrogen anti-periplanar to the iodine.



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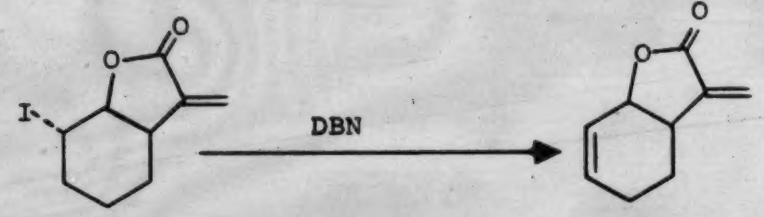
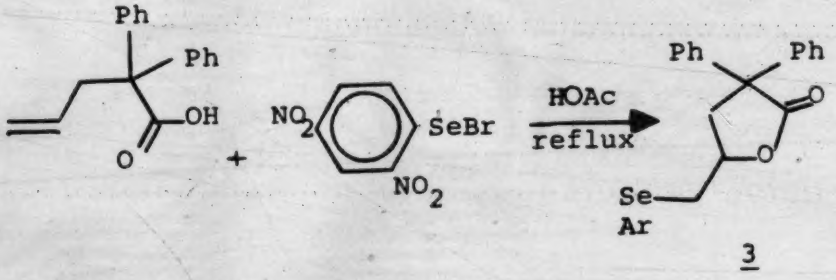


(3)[11]

Although halolactonization has proved invaluable in synthetic chemistry, limitations are evident. In particular, the requirement of performing the reactions in aqueous basic media,[12] and the severe conditions to which some iodolactones must be subjected for conversion to other substrates, have promoted the search for alternative methods to effect such operations.

Selenium as an Electrophile

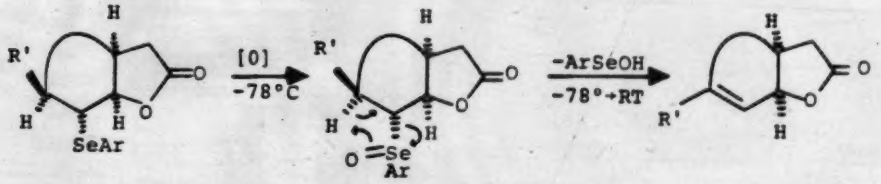
In 1960 de Moura Campos[13] demonstrated that an unsaturated acid could be lactonized to the corresponding 5-membered lactone using an aryl-substituted selenenyl bromide (eq. (4)). Unfortunately the harsh conditions required to lactonize the acid (specifically chosen because of its facile ability to lactonize[14]) and the non-utility of the selenolactone itself, completely eliminated any synthetic use of such a reaction at the time of its discovery.



3 (4)

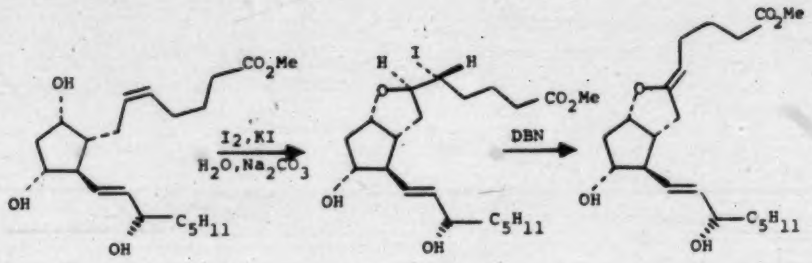
The advent of the selenoxide fragmentation in 1973, realized in this laboratory[15] and independently by other

workers,[16] succeeded in giving the reaction summarized in eq. (4) synthetic viability. Provided that milder means could be found to make selenolactones such as 3 , selenoxide fragmentation of the selenide would provide an excellent alternative to the basic elimination of hydrogen iodide from iodolactones. In contrast to the elimination of hydrogen iodide, the selenoxide fragmentation requires a cis hydrogen for elimination and fragmentation prefers to occur away from oxygen, thus removing the less acidic proton (eq. (5)). While cyclizations



(5)

with either iodine or selenium reagents often lead to similarly substituted compounds, subsequent conversion to the unsaturated analogue can result in different products being formed, reflecting the mechanistic differences between the two methods. An example of such an occurrence is shown in equations (6) and (7).



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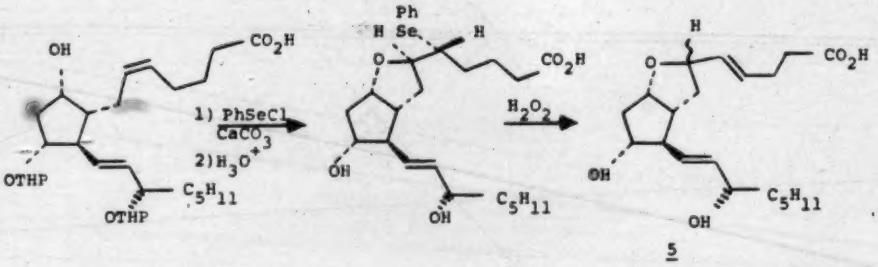
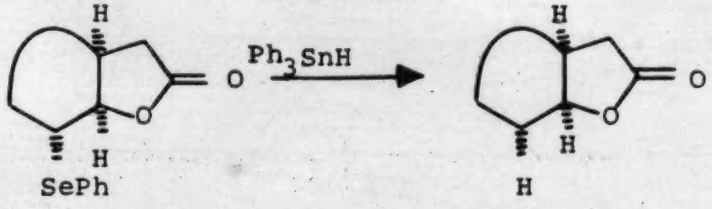


(7)[18]

5

While cyclization with iodine and elimination results in formation of the trisubstituted olefin 4 , cyclization using selenium followed by selenoxide fragmentation gives the disubstituted olefin 5.

Additional increases in the versatility of the selenolactone, such as the efficient reduction to the saturated lactone using triphenyltin hydride[19] (eq. (8))



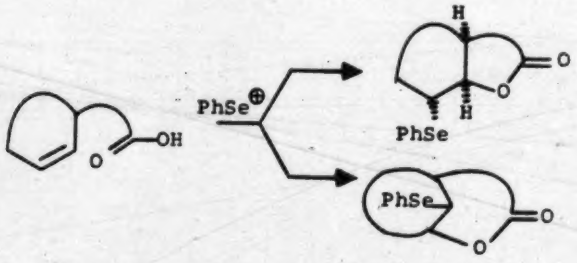
(8)

and the rapidly developing diversity of selenium chemistry,[1] has served to make the selenolactone a potentially valuable synthetic intermediate. In view

of this, it was decided that a useful contribution could be made if an efficient method could be demonstrated for the preparation of selenolactones such as 3 .

Results and Discussion

We have investigated the lactonization of unsaturated acids with benzeneselenenyl chloride[20] and have found that cyclofunctionalization[21] can be effected under mild conditions, resulting in moderate to high yields of the corresponding lactones (eq. (9)). Furthermore we have found that the process appears to be general in its application to unsaturated acids.[22,23]



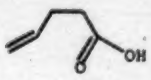
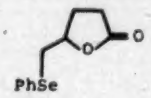
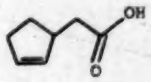
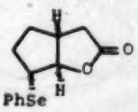
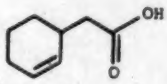
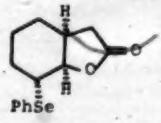
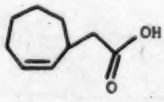
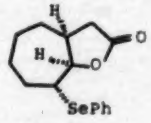
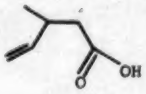
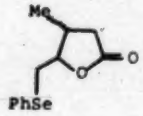
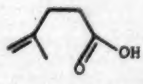
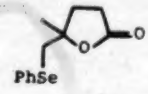
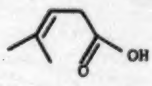
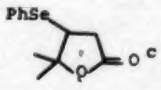
(9)

While the experimental procedure requires exclusion of moisture, the technique is relatively simple. As a general procedure benzeneselenenyl chloride (one equivalent) was dissolved in a suitable solvent and the solution was added dropwise to a stirred solution of the acid in the same solvent. Some of the more convenient solvents which were employed are: diethyl ether, ethyl

acetate, dichloromethane, chloroform and carbon tetrachloride. The reaction mixture was usually stirred overnight at room temperature prior to work-up although some acids (6 and 8) required additional heating (80°C, 2-4 h) to effect complete lactonization (TLC and/or IR control). After lactonization was essentially complete the solvent was evaporated and the residue was chromatographed over silica gel. Direct chromatography of the residue from the reaction mixture is desirable since we have observed that reactions which have not gone to completion (IR control) can still result in high yields of lactones if chromatographed over silica gel.[24] Since all of the reactions went to completion if longer reaction times or heating were employed, this catalytic effect was not examined in more detail.

The preparative results from the cyclofunctionalization of various acids with benzeneselenenyl chloride are summarized in Table I. The structures of the lactones were deduced using spectroscopic methods and their constitutions were confirmed by elemental analysis. Most relative configurations were determined by extensive ^{1}H-NMR decoupling and subsequent examination of Dreiding models. To further confirm the structures shown for 7a, 8a , 9a and 15a, the lactones were treated with triphenyltin hydride causing the replacement of the phenylseleno- group

Table I: Cyclofunctionalization Products.

Starting Acid		Product		(%)
6		6a		94%
7		7a		73%
8		8a		82%
9		9a		97%
10		10a		~69%[a]
11		11a		85%, 95%[b]
12		12a		[c]
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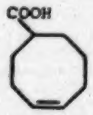
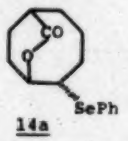
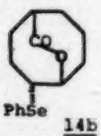
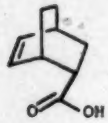
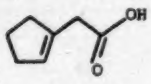
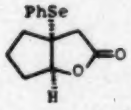
(continued...)

Table I (continued)

14		 +  14a 14b	87%[d]
15		15a[e]	76%
16		 16a	30%

[a] A 1:1 mixture of isomers is formed. Cf. Bartlett, P.A.; Myerson, J. J. Am. Chem. Soc., 1978, 100, 3950.

[b] 95%: corrected for impurity in 11.

[c] The starting acid 12 was an impurity in 11 and compound 12a was isolated in ~80% yield (based on the amount of 12 in 11 and assuming no isomerization, 11 → 12).

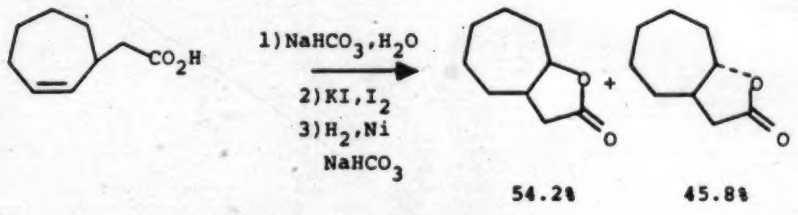
[d] Combined yield. Initially isolated proportions were: 14a:14b:4:1.

[e] See Adams, T.; Moriarty, R.M. J. Am. Chem. Soc. 1973, 95, 4071.

by hydrogen[19] (eq. (8)). The resulting products were then identified by comparison with authentic samples.

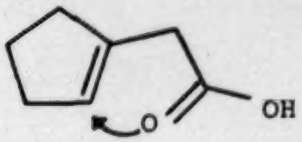
The spectral data for 14a and 14b were not definitely diagnostic and the assignments made from our experiments were tentative. Independent work[22c] has confirmed these assignments.

The bicyclic lactones 7a , 8a , 9a and 16a in Table I demonstrate that ring closure occurs in a manner so as to give cis ring fusion. A similar effect has also been observed for halolactonization, although for rings possessing more than six carbons, halolactonization can result in a mixture of cis and trans lactones.[25] For example, while cyclofunctionalization of 9 gave only the cis-lactone 9a , iodolactonization of 9 gave a 1:1 mixture of both cis and trans lactones[26] (eq. (10)).



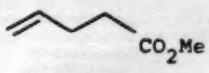
(10)

The low yield obtained for 16a sharply contradicts the trend expressed by the other examples in Table I. This low yield may be a reflection of the fact that ring closure is formally proceeding through a 5-endo process 17 which is a disfavored course according to the Rules for Ring Closure.[27]

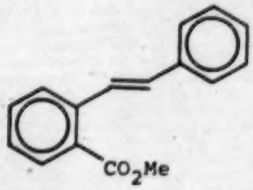


17

During the course of this work a number of alternative procedures for cyclofunctionalization of unsaturated acids were examined. Treatment of esters 18 or 19 with benzeneselenenyl chloride did not result in any lactone product.[28] Likewise, the silyl ester 20 in diethyl ether

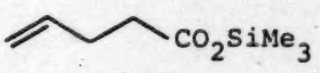


18

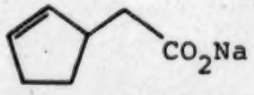


19

or the acid salt 21 in tetrahydrofuran failed to produce the corresponding selenolactones efficiently when mixed with benzeneselenenyl chloride. The cyclofunctionalization



20



21

Et2NSePh

22

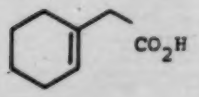
of acid 6 with N,N-diethylbenzeneselenenamide 22[29] was found to be extremely fast, however this reaction was not as clean as the usual procedure, resulting in

the formation of side-products which were difficult to remove. Lactone formation was observed (IR) when 6 was treated with benzeneselenenyl trichloride,[30] however this course of action offered no advantages over the use of benzeneselenenyl chloride. Finally, the use of 2,4-dinitrobenzeneselenenyl chloride[31] was examined; the reaction of this reagent with 7 in chloroform failed to produce any substantial amount of lactone.

Mechanistic Considerations

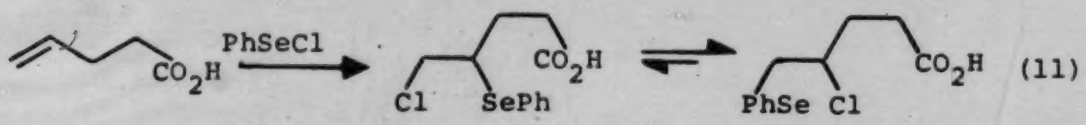
During our studies most of the reactions were examined periodically for completeness by removing a small aliquot from the reaction mixture and inspecting its IR spectrum. While all of the starting materials reacted rapidly with benzeneselenenyl chloride causing discharge of the orange color due to the reagent, very little, if any of the final product could be detected spectroscopically (IR). In most cases the only carbonyl absorption in the IR spectrum, taken immediately after decoloration of the selenium reagent, was that corresponding to a carboxylic acid (1710 cm^{-1}). In addition to this observation, IR spectra taken periodically throughout the reaction usually revealed the formation of a band at ca. 1740 cm^{-1} (see Table II) prior to formation of the γ-lactone band of the final product. As the reaction continued, the γ-lactone band of the final product slowly increased until, at the

TABLE II: INTERMEDIATE IR BANDS DURING CYCLOFUNCTIONALIZATION (±5 cm^{-1}).

STARTING ACID	IR BANDS IN CARBONYL REGION (cm^{-1})	SOLVENT
6	1710, 1742, 1770	$CHCl_3$
7	1710, 1738, 1768	$CHCl_3$
8	1709, 1754, 1775	$CHCl_3$
9	1710, 1770, 1785	$CHCl_3$
10	1710, 1735, 1788	CCl_4
11	1710, 1753, 1766	$CHCl_3$
15	- , - , 1770	$CHCl_3$
16	1710, (1743), 1765	CH_2Cl_2
 (23)	1710, (1753), 1772, 1782	CH_2Cl_2

completion of the reaction, it was the only band present in the carbonyl region of the IR spectrum.

In order to attempt to elucidate the apparent intermediates of the reaction, NMR studies were performed on acids 6 , 7 , 8 , 9 and 10 in Table I. For all of the examples studied, with the exception of 6 , the spectra were too complex to interpret in a decisive manner. The NMR spectra for the cyclofunctionalization of 6 however, were the least complex and were amenable to partial interpretation. The spectra indicate that benzeneselenenyl chloride first adds across the double bond kinetically to give the β-chloroselenide 24 in equation (11). The selenide 24 then rearranges to the thermodynamically more stable isomer 25 prior to any formation of lactone.[32] Unfortunately, subsequent alterations in the spectra could not be deciphered.

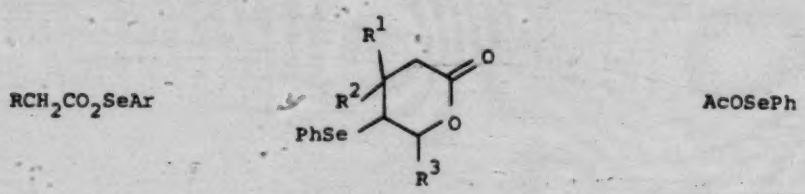


24 25

It is likely that for all of the examples studied by NMR benzeneselenenyl chloride adds across the double bond in a fashion similar to that with 6 since the immediate disappearance of olefinic protons without concomitant loss of carboxylic acid proton was observed in each case.

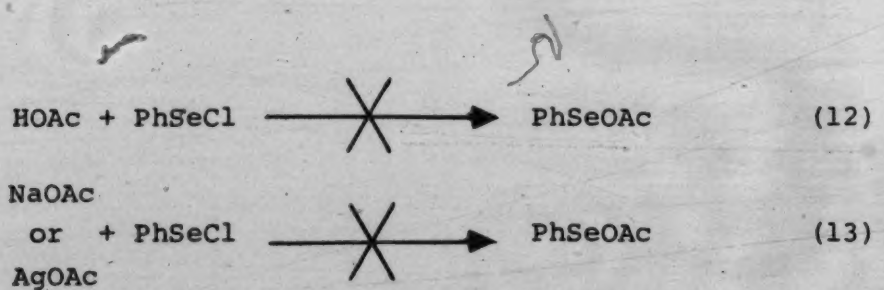
Despite repeated attempts, the intermediate responsible for the absorption at ca. 1740 cm^{-1} in the IR spectrum could not be isolated from any of the examples studied. Therefore, the nature of the intermediate can only be surmised.

An inspection of the possibilities revealed that there are two likely chromophores which could give rise to such a band in the IR spectrum. These are the seleno-carboxylate 26 (Ar = Ph) and the δ-lactone 27. While selenocarboxylates such as 26 have been reported[33]



26 27 28

there is evidence that these compounds are unstable. Although the selenocarboxylate 28 has been referred to in the literature,[33a] it has never been isolated and attempts to prepare it in this laboratory were not successful (eq. (12) and (13)). Acetic acid failed to react with

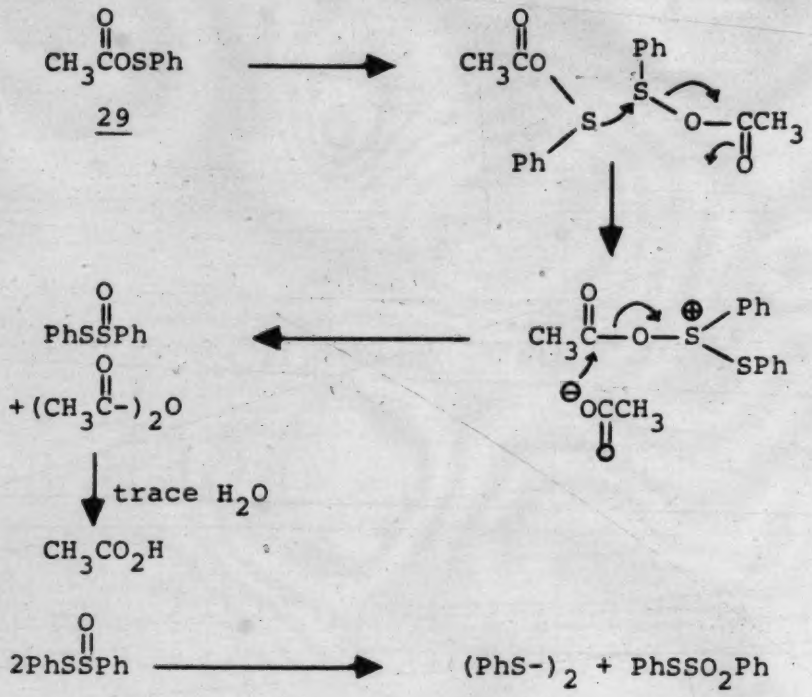


benzeneselenenyl chloride (eq. (12)), while the product isolated from the experiment summarized by equation (13) proved to be diphenyldiselenide. When the reaction mixtures corresponding to equation (13) were monitored (solution IR) for the presence of 28 in solution, the spectra indicated the presence of three bands in the carbonyl region at 1810, 1765, and 1710 cm^{-1}. An explanation for this phenomenon can be provided by examining analogous work on phenylsulfenylcarboxylates. Hogg[34] has shown that the addition of sodium acetate to benzenesulfenyl chloride in carbon tetrachloride results in the formation of acetic anhydride and acetic acid in addition to diphenyldisulfide.[35] It has been suggested that these products result from the formation and subsequent thermal decomposition of phenylsulfenylacetate 29. The mechanism of this decomposition has been postulated to be that shown in Scheme I. Since acetic anhydride and acetic acid were detected spectroscopically it seems reasonable that 28 is also thermally unstable and therefore undergoes decomposition in a similar fashion.

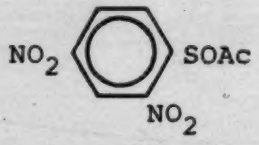
PhSOAc

29

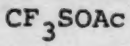
Scheme I



Stable sulfenylacetates can be made if the phenyl group attached to the sulfur atom is substituted with electron-withdrawing substituents or replaced with electron-withdrawing moieties,[36] examples being 30 and 31.

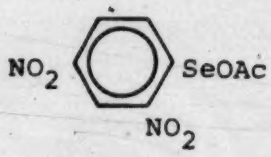


30



31

Similar compounds with selenium have also been prepared,[33,37] although the number of examples are few. One such example is 32 .

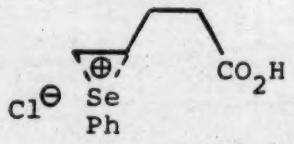


32

Unfortunately spectral data for selenoacetates such as 32 have never been published.[38] As a result the $IR_{\nu C=0}$ frequencies for this type of chromophore could not be examined. In any case, it is unlikely that the $IR_{\nu C=0}$ of 32 would be representative of compounds such as 26 (Ar = Ph) since data[36] collected on the corresponding sulfenylcarboxylates reveals a high dependence of the $IR_{\nu C=0}$ frequency on the nature of the particular substrate, with values ranging from 1710 cm^{-1} to 1780 cm^{-1}.

The apparent instability of 28 and the inert behavior displayed by benzeneselenenyl chloride towards acetic acid renders the selenocarboxylate 26 (Ar = Ph) an unlikely candidate for the intermediate responsible for the 1740 cm^{-1} band in the IR spectrum. If the selenocarboxylate 26 (Ar = Ph) was being formed at least in part by direct displacement of chlorine by the carboxylic acid then the reaction displayed in equation (12) should have produced a band in the IR spectrum at ca. 1740 cm^{-1}. This did not occur. On the other hand, this apparent discrepancy in reactivity between the unsaturated acids in Table I and acetic acid could be resolved if one inferred that

benzeneselenenyl chloride was being activated towards nucleophilic displacement in the presence of the unsaturated acids. It is likely that addition of benzeneselenenyl chloride across the double bond, which was shown by NMR studies to occur prior to lactonization, results in a species such as 33[39] in which the benzeneseleno- group



33

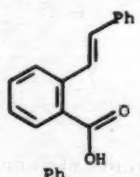
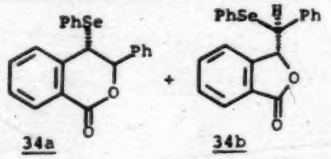
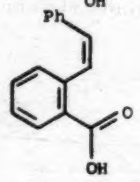
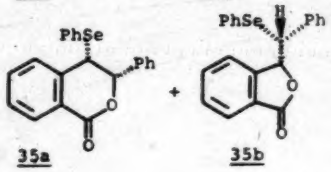
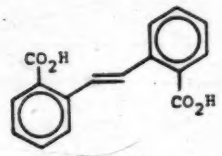
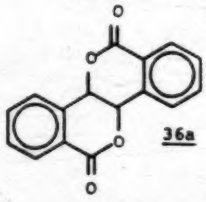
might be more susceptible towards nucleophilic displacement. This would then account for the possible formation of 26 (Ar = Ph) with unsaturated acids but not with acetic acid.

If this hypothesis is correct then the salt of an unsaturated acid would also be expected to result in the appearance of an intermediate band when treated with benzeneselenenyl chloride, eventually yielding the desired lactone. However, as noted previously, the reaction of 21 with benzeneselenenyl chloride did neither. None of the lactone 7a was detected (TLC control) and an IR spectrum of the residue from the reaction mixture after solvent evaporation revealed the presence of three bands in the carbonyl region at 1772, 1725 and 1702 cm^{-1}. Since all of the benzeneselenenyl chloride was consumed during

the reaction (color dissipation) it can be concluded that use of the sodium salt 21 instead of 7 altered the entire course of the reaction. It is possible that by using the salt 21 condensation to give 26 (Ar = Ph) occurred, which then underwent decomposition as depicted in Scheme I thus producing the three carbonyl bands in the IR spectrum.

The possibility that the δ-lactone 27 may be responsible for the 1740 cm^{-1} band in the IR spectrum was shown by the cyclofunctionalization of acids 34 , 35 and 36 in Table III. When the cyclofunctionalizations of 34 or 35 were monitored using IR spectroscopy both acids produced an intermediate band (ca. 1738 cm^{-1}). However, in contrast to the examples in Table I, these acids produced a very high concentration of the intermediate (IR control) prior to the appearance of secondary product. As shown in Table III, for both acids 34 and 35 work-up of the reaction mixtures resulted in the isolation of the secondary product as well as the product responsible for the intermediate band in the IR spectrum. Confirmation that δ-lactone 34a was responsible for the intermediate band was obtained by an NMR study of the reaction. The study revealed the rapid appearance of signals due to the δ-lactone 34a, these then decreased (with respect to the total aromatic signals) and there

TABLE III. Cyclofunctionalization Products.

Starting Acid	Product (%)
34 	 89%[a]
35 	 79%[b]
36 	 87%[c]

[a] Combined yield. Initially isolated proportions were: 34a:34b:2:3. Assumed (mechanistically) stereochemistry.

[b] Combined yield. Initially isolated proportions were: 35a:35b:3:1. Assumed (mechanistically) stereochemistry.

[c] Stereochemistry of the ring junctions could not be readily determined.

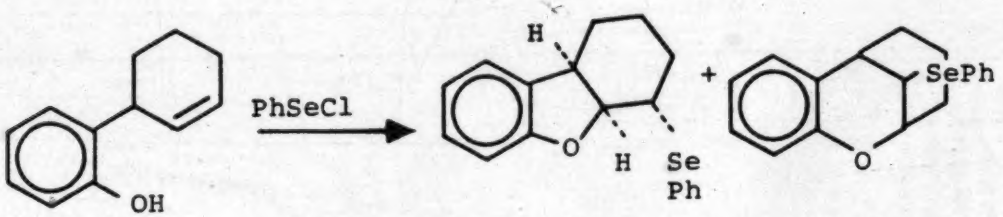
was a corresponding increase in the signals due to the γ-lactone 34b (see Table IV).

When the pure δ-lactone 34a was treated with approximately one equivalent of HCl in dry ether, it was converted into the γ-lactone 34b, thus verifying that for the cyclofunctionalization of acid 34 with benzeneselenenyl chloride the δ-lactone 34a is the kinetic product of the reaction and the γ-lactone 34b is the thermodynamic product.[40] The isolation of kinetic and thermodynamic

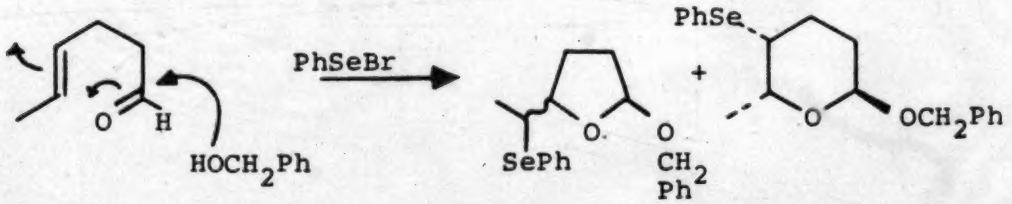
Table IV: ^{1}H-NMR Integration Values

Time(h)	Total Aromatic—H	Total HOC—H	34a PhSeC—H	34b PhSeC—H
0.12	14.19	0.89	0.90(98%)	0.02(2%)
0.58	14.18	0.89	0.84(91%)	0.08(9%)
2.0	14.14	0.92	0.74(80%)	0.19(20%)
8.0	14.17	0.91	0.54(59%)	0.37(41%)
22	14.36	0.83	0.37(45%)	0.45(55%)

products from the cyclofunctionalization with selenium reagents has been observed before.[41] The examples are shown in equations (14) and (15). For both of these examples



(14)



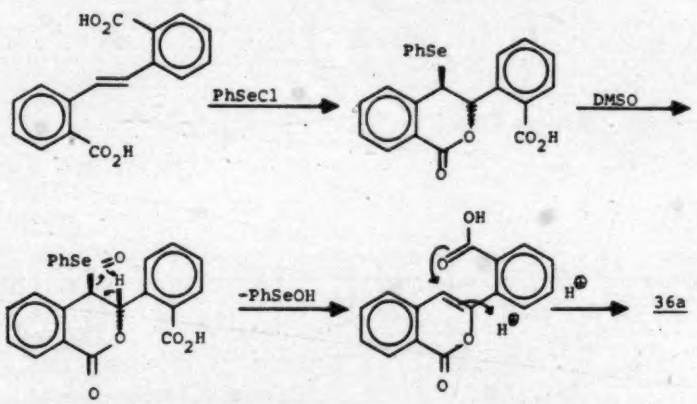
(15)

the kinetic product is the 5-membered cyclic ether and the thermodynamic product is the 6-membered cyclic ether.[42]

Although it is with less certainty, the cyclofunctionalization of 36 in Table III also appears to proceed

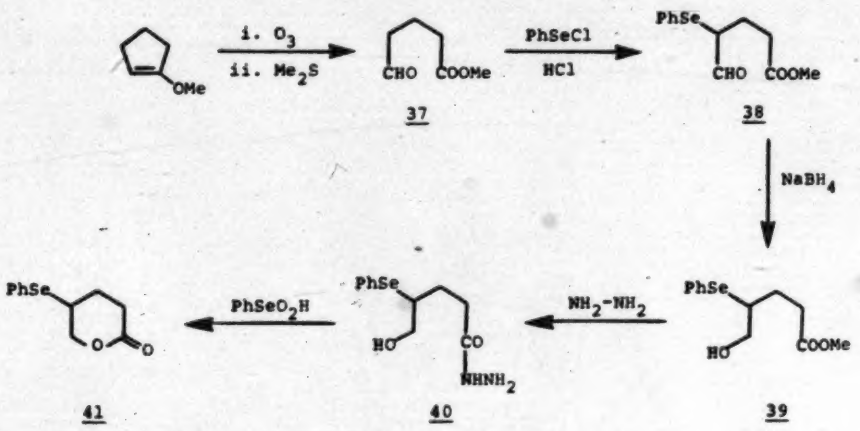
through a δ-lactone. Because of solubility reasons the reaction of 36 with benzeneselenenyl chloride was carried out in dimethylsulfoxide. After stirring the reaction mixture overnight a white precipitate was obtained which was subsequently characterized to be 36a. The formation of 36a is probably due to the series of reactions depicted in Scheme II.[43]

Scheme II

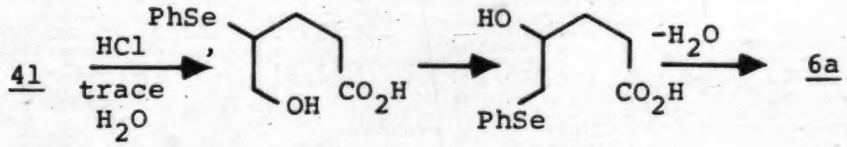


To obtain more evidence in support of the possibility that a δ-lactone is a general intermediate in the cyclofunctionalizations of the acids in Table I, the δ-lactone 41 was prepared[44] (Scheme III) and its properties were examined. When the δ-lactone 41 was treated (under anhydrous conditions) with HCl in ether, substantial rearrangement to the γ-lactone 6a resulted. Evidence that the rearrangement did not occur via the β-hydroxyselenide

Scheme III

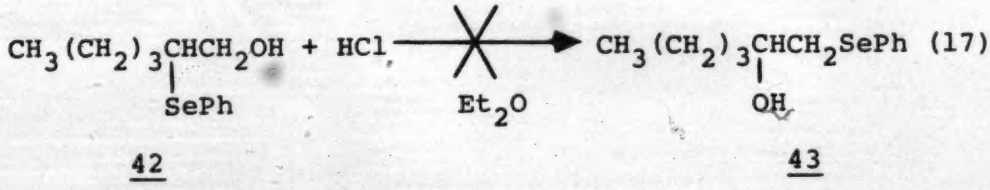


followed by subsequent closure to 6a (eq. (16)) was provided by the experiment summarized in equation (17). Thus treat-



(16)

ment of 42 with HCl under conditions similar to that for 41 did not result in the formation of 43.

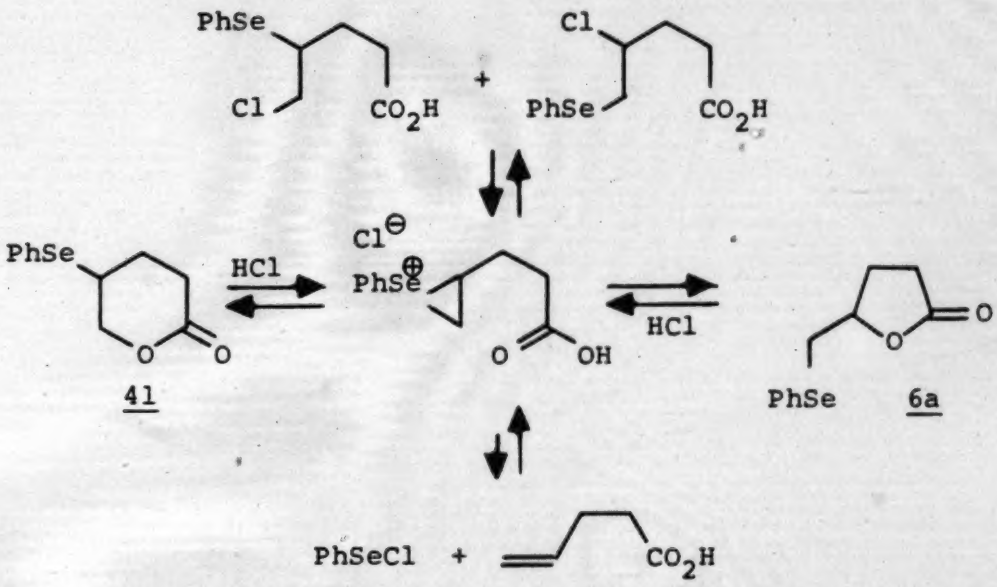


(17)

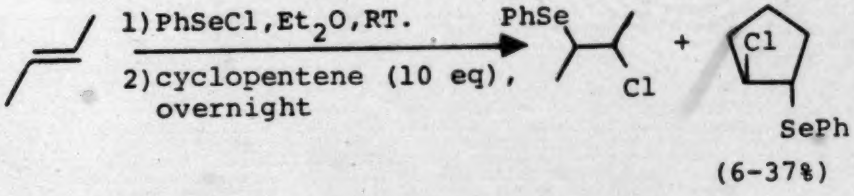
A chemically reasonable mechanism for the rearrangement of 41 to 6a , assuming anhydrous conditions, is shown in

Scheme IV. The reversible addition of benzeneselenenyl chloride across a double bond (as indicated in Scheme IV)

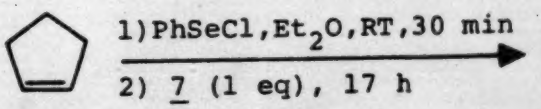
Scheme IV



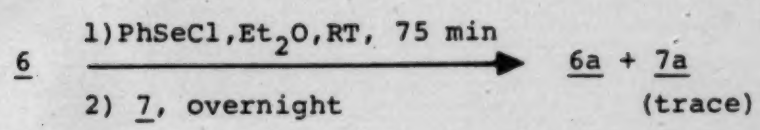
has been demonstrated by the reactions summarized in equations (18), (19) and (20) inasmuch as partial exchange



(6-37%) (18)

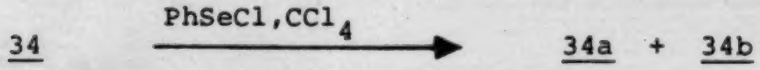


31% (NMR) (19)

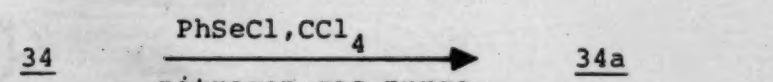


(20)

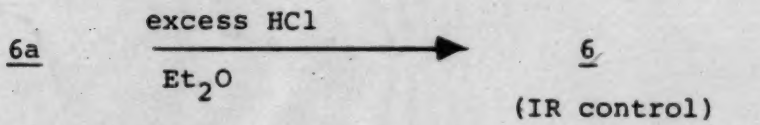
was observed in all three experiments. The importance of HCl indicated in Scheme IV has been exemplified by the reactions summarized in equations (21), (22) and (23). Equations (21) and (22) demonstrate that removal of HCl (by a nitrogen gas purge) serves to prevent formation of



(21)



(22)

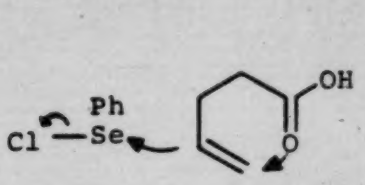


(23)

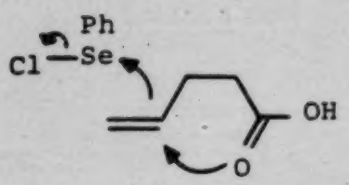
the thermodynamically more stable product 34b, while equation (23) demonstrates that addition of excess HCl to 6a causes ring opening to the unsaturated acid 6. The

facility by which these rearrangements can occur under acidic conditions was demonstrated by 14a and 14b. On storage in deuterated chloroform the individual lactones were converted to a mixture of both isomers, presumably by the presence of acid traces.

While it has not been clearly established whether cyclofunctionalizations occur via an episeleniranium ion[39] (e.g., 33) or by a concerted process[45] (e.g., 44 or 45) it is likely that open ions are not involved because of the clean antarafacial addition of benzeneselenenyl chloride to double bonds.



44



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Conclusion

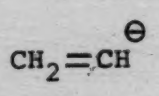
Cyclofunctionalization of unsaturated acids is a reaction of general application which can be carried out under mild conditions. The high yields and versatility of the selenolactone should make this type of reaction an attractive process in synthetic methodology.[23,46]

While it was not the initial purpose of this investigation, the mechanism of this reaction has been examined and some of the inherent features have been

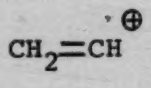
ascertained. It appears that the reaction involves the formation of several intermediates prior to formation of the final product. For some cases these intermediates have been identified. It has been shown that the formation of a δ-lactone in most of these reactions is a plausible explanation for the appearance of a band at ca. 1740 cm^{-1} in the IR spectrum. The kinetic formation of a δ-lactone during the cyclofunctionalization of 34 has been proven. Attempts to prepare and examine selenocarboxylates such as 26 and 28 were unsuccessful. Although unlikely, the possibility that this type of chromophore might be responsible for the 1740 cm^{-1} band cannot be ruled out.

VINYL CATION SYNTHON

The vinyl anion 46 is a readily obtainable[47] and synthetically useful reagent in organic synthesis. In contrast, its counterpart, the vinyl cation 47 has seen little or no use in the preparative sense, in spite of



46



47

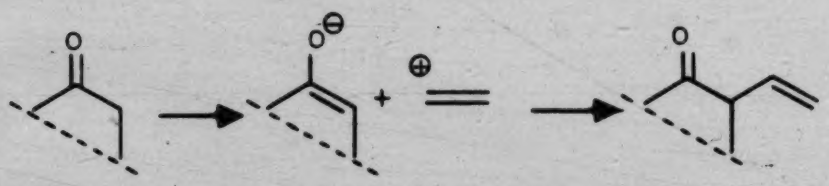
its synthetic value.[48] The absence of the vinyl cation in preparative organic synthesis originates from the instability of the substrate itself. Cations of this type are difficult to generate, and once formed, are extremely reactive.[49] As a consequence, these species have only been demonstrated as intermediates in solvolysis reactions.

The increasing interest in macrolide chemistry[5] in addition to theoretical and commercial interests in large ring compounds has served to emphasize the potential utility of the vinyl cation as a synthetic unit. The procedures currently available to prepare large ring compounds can be generally classified into three categories: Grob-type fragmentation of smaller bicyclic systems; cyclization of long acyclic compounds; and ring

expansion of existing carbocyclic rings. Of the three procedures, the first two have demonstrated only limited success, and the last approach is viewed as being the most favorable.[5b]

The known methods of ring expansion are diverse,[50] among which the most efficient are the Cope,[51] oxy-Cope[52] and Cope-Claisen[53] rearrangements, since these reactions involve the incorporation of four carbon units into the ring-expanded product[54] (see Scheme V).[55] In addition to their efficiency, such electrocyclic processes have well defined and often predictable stereochemical outcomes, thus adding to their versatility.

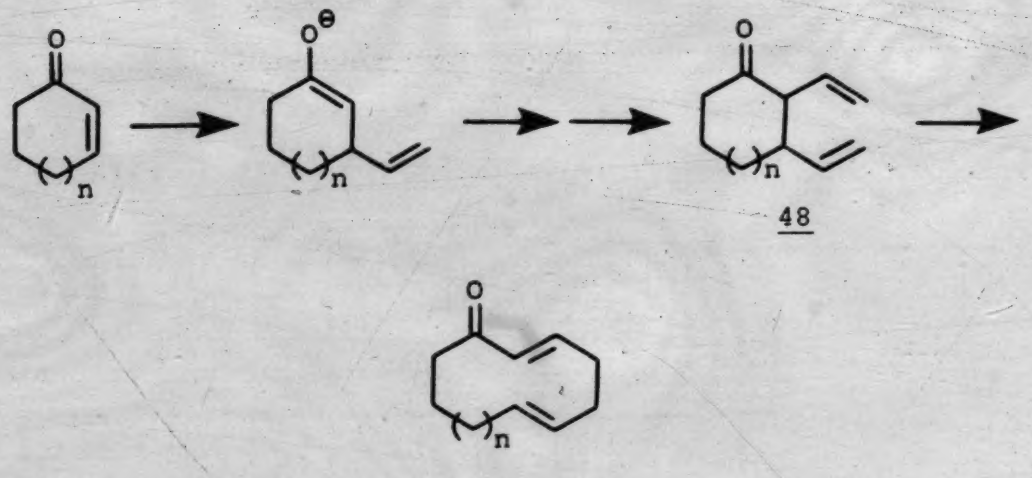
In order to construct precursors such as 48 and 49 (Scheme V) an efficient method for the construction of α-vinylketones (formally represented as the addition of an enolate to a vinyl cation, equation (24)) would be useful. Work by Kato[56] and Watanabe[57] has shown that



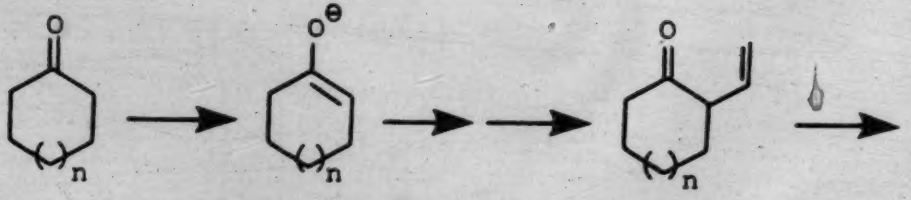
(24)

substrates such as 50 can be prepared by treatment of α-chloroketones with excess vinylmagnesium chloride (eq. (25)), however, the method is extremely sensitive to

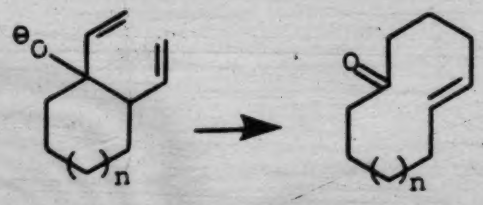
Scheme V

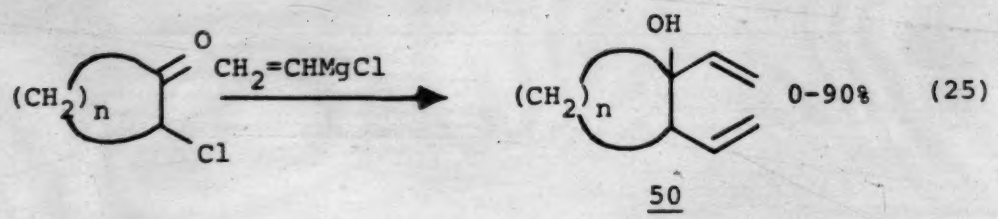


48



49



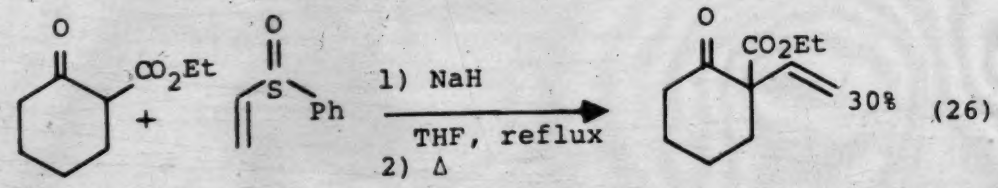


50

ring size and gives respectable yields only for six and seven membered ketones (n = 4, 5).

In response to the challenge to make vinyl cations accessible for organic synthesis a number of authors have examined the possibility of using vinyl cation synthons.[58] As a result of these investigations two methods have been developed which display practical application to the synthesis of substrates such as 48 and 49 .

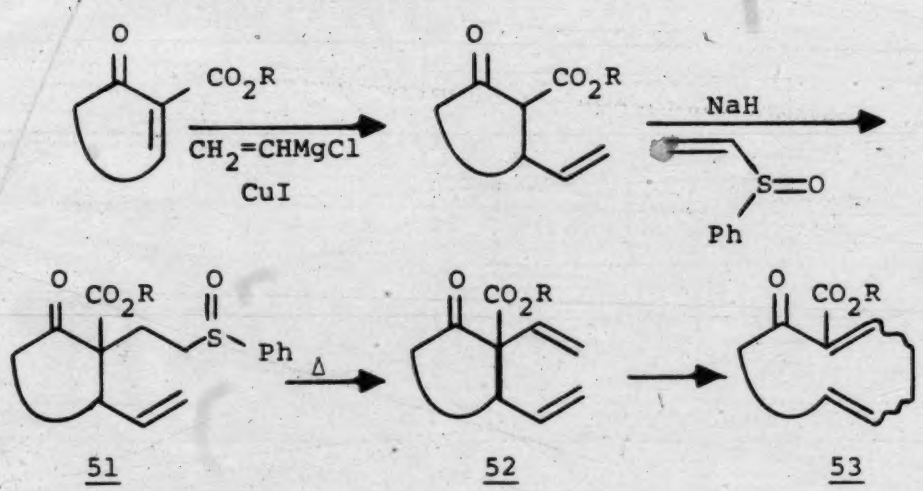
In 1975 Koppel established that condensations between enolates and phenyl vinyl sulfoxide could be effected,[58a] resulting in compounds which upon heating yielded the desired α-vinylketone (eq. (26)). While yields were



modest, a recent application of this method to ring expansion methodology was provided by Heimgartner[58b] in 1979. The procedure used for the ring expansions is

outlined in Scheme VI . Despite its apparent attractiveness the procedure had a serious limitation in that the

Scheme VI

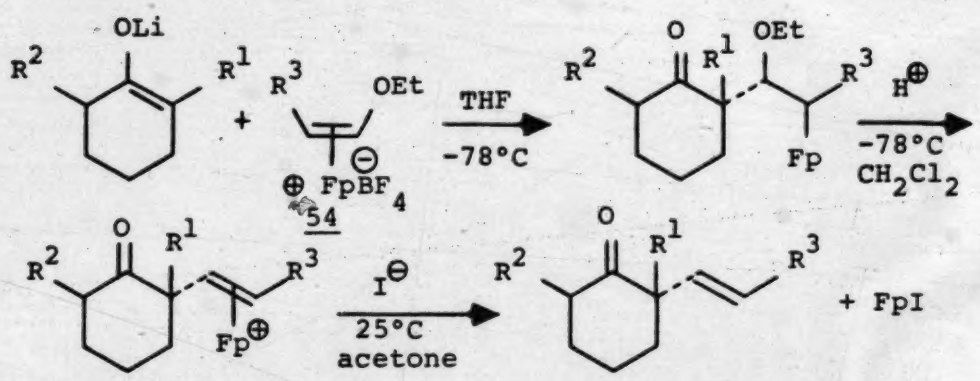


51 52 53

condensation to give 51 often resulted in very poor regioselectivity. In most of the examples studied the required isomer (51) was the minor product from the condensation. As a result the yields of diene 52 and/or ring expanded product 53 were usually no higher than 20-25%.

During the course of our investigation a more viable vinyl cation synthon was reported by Rosenblum[58g] which employed the use of Fp (vinyl ether) complexés [Fp = $C_5H_5Fe(CO)_2$]. Demonstrated in Scheme VII , the procedure appears to give good yields of the olefinic material

Scheme VII



i) $R^1 = R^2 = R^3 = H$

ii) $R^1 = R^3 = H, R^2 = Me$

iii) $R^1 = Me, R^2 = R^3 = H$

iv) $R^1 = R^3 = Me, R^2 = H$

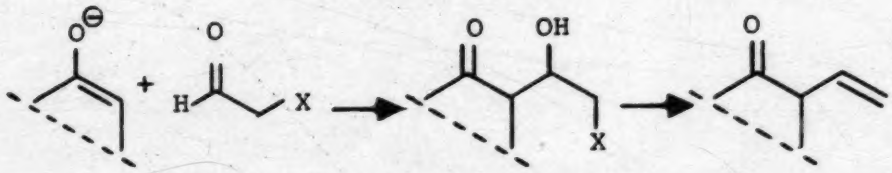
(68-88%). Unfortunately, the known examples of this method are currently restricted to the four shown in the scheme. The only disadvantage to using this procedure seems to be the preparation of the reagent, 54[59] which requires preparation, handling and storage under an inert atmosphere to prevent oxidative decomposition.

Phenylselenoacetaldehyde

Of the several potential approaches to synthetic equivalents for the vinyl cation, we chose to examine the

method summarized in Scheme VIII , which relies on the well established aldol condensation to generate a properly substituted intermediate 55 , such that it can then be converted into the required olefin 56 . An examination of the literature revealed that the conversion of β-substituted alcohols (HO-C-C-X) into olefins is a known

Scheme VIII



55 56

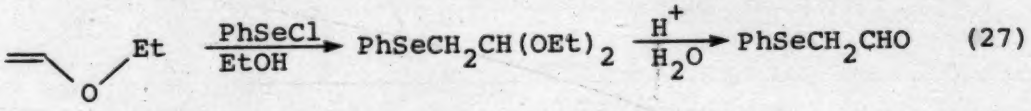
process for X = Si,[60] P,[61] and Se.[1a] As a result, we initially examined the use of aldehydes 57 , 58 and 59 , shown below.

Me_3SiCH_2CHO $(EtO)_2POCH_2CHO$ $PhSeCH_2CHO$

57 58 59

Of the three aldehydes, 57 proved to be extremely difficult to prepare and therefore was not suitable for further study. Preliminary experiments to effect aldol condensations with 58 gave poor results, hence the use of this aldehyde was also deemed to be inappropriate. In contrast to the other examples, phenylselenoacetaldehyde 59 was observed to undergo aldol condensation efficiently,

resulting in the isolation of the aldol product 55 (X = SePh) in high yields. This, together with the ease of preparing the aldehyde[62] (eq. (27)) and the already



(27)

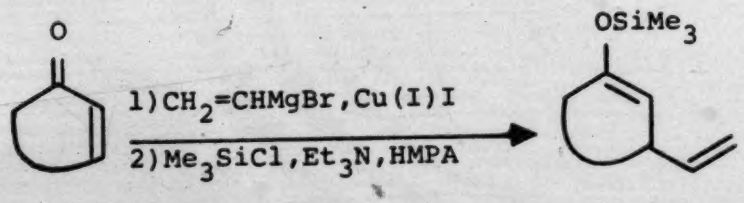
established methods for conversion of β-hydroxyselenides into the corresponding olefins,[1a] served to satisfy the criteria required for a vinyl cation synthon. Therefore, a detailed examination of the use of phenylselenoacetaldehyde as a vinyl cation synthon was carried out and the results are discussed in the following section.

Results and Discussion

In order to realize optimum yields of the ketohydroxyselenides 55 (X = SePh) most of the condensations performed during our investigation were carried out using zinc enolates[63] as this method has been shown to displace unfavorable equilibria and reduce side reactions such as polycondensation and dehydration. The zinc enolates were obtained by adding a measured volume of saturated ethereal zinc chloride[63a] to a cold solution of the corresponding lithium enolate. For most examples, 0.5 mole of zinc chloride was used per mole of lithium enolate.

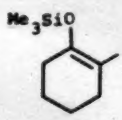
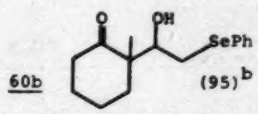
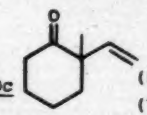
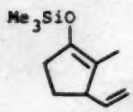
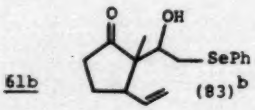
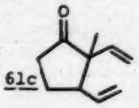
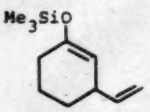
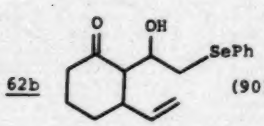
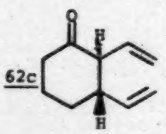
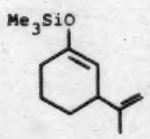
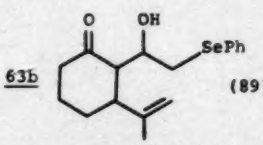
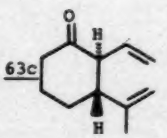
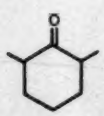
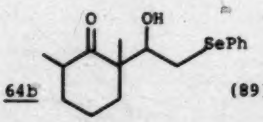
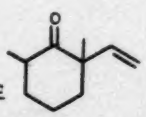
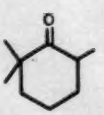
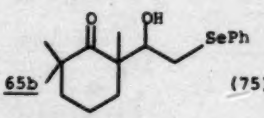
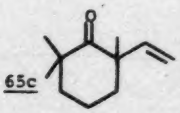
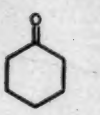
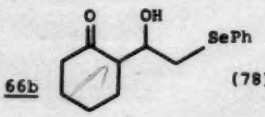
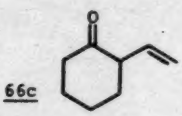
The lithium enolates were in turn prepared by either deprotonation of ketones using lithium diisopropylamide or by addition of methyllithium to the corresponding silyl enol ethers.[64] Of the two methods, the latter was judged to be superior since the reactions of enolates generated in this fashion were always clean and gave high yields of the ketohydroxyselenides. In view of the recent interest in the use of enol borinates[65] we also examined the feasibility of using these substrates to effect condensations with phenylselenoacetaldehyde.

The results of the various condensations have been summarized in Table V . As in the previous section, the structures shown were deduced using spectroscopic methods and their constitutions were confirmed by elemental analysis. Most relative configurations were determined by extensive ^{1}H-NMR decoupling and subsequent examination of Dreiding models. The silyl enol ethers 61a, 62a and 63a were prepared by trapping the enolate formed from conjugate addition of a magnesium cuprate with chlorotrimethylsilane (eq. (28)). The silyl enol ethers were then cleaved with methyllithium to generate the corresponding lithium enolates.



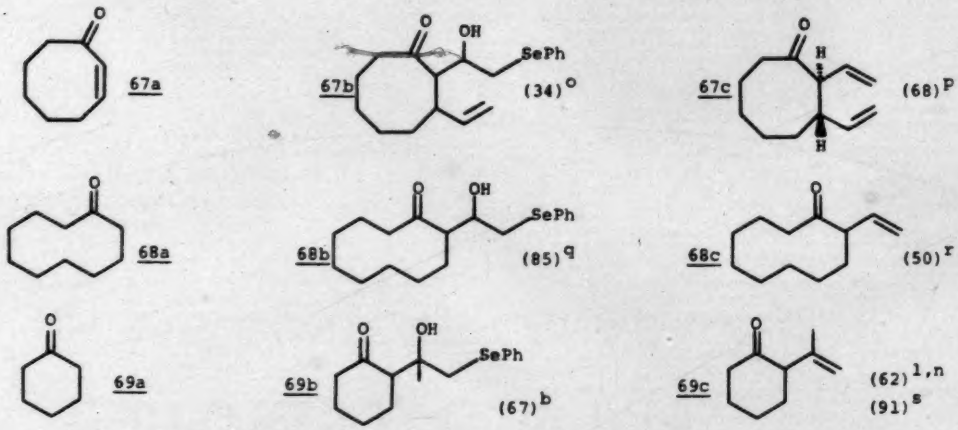
(28)

TABLE V: Ketohydroxyselenide and α-Vinylketone Products.[a]

Starting Material	Condensation Product (%)	Olefin (%)
 60a	 60b (95)[b]	 60c (82)[c] (78)[c,d]
 61a	 61b (83)[b]	 61c (82)[e] (84)[f]
 62a	 62b (90)[b]	 62c (82)[g]
 63a	 63b (89)[h]	 63c (89)[i] (80)[j]
 64a[b]	 64b (89)[b]	 64c (75)[k,l]
 65a	 65b (75)[b]	 65c (84)[l,m] (98)[d]
 66a	 66b (78)[b]	 66c (54)[l,n]

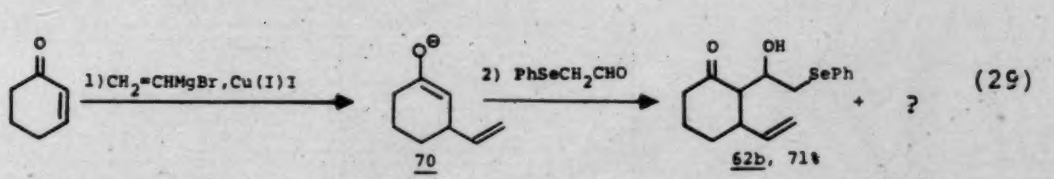
(continued...)

TABLE V. (continued)



[a]Yields refer to isolated material, except where indicated Except for structures 62c, 63c, 67c, the formulas are not intended to have stereochemical implications. [b]Mixture of diastereoisomers. [c]The precursor was the crystalline diastereoisomer. [d]$COCl_2$-NaI method. Yield determined by NMR. [e]97% pure by VPC. High R_f hydroxyselenide used. [f]99% pure by VPC. Low R_f hydroxyselenide used. [g]97.5% pure by VPC. High R_f hydroxyselenide used. [h]Combined yield of the separated isomers. [i]>99% pure by VPC. High R_f hydroxyselenide used. [j]>98% pure by VPC. Low R_f hydroxyselencide used. [k]>98% pure by VPC. [l]Diastereoisomeric mixture of hydroxyselenides used. [m]>99% pure by VPC. [n]Yield determined by NMR. [o]One (>97%) diastereoisomer. [p]>97% pure by VPC. [q]One (>98%) diastereoisomer. [r]>99% pure by VPC. [s]After correction for recovered starting material.

Direct condensations of enolates derived from conjugate addition with organocuprates have been demonstrated;[66] however we preferred to trap the enolate to avoid any possible side products due to enolate equilibration and/or polycondensation that have occasionally been observed using the direct condensation method.[67] When the synthesis of 62b was attempted by direct condensation of the enolate 70 with phenylselenoacetaldehyde (eq. (29)), the desired ketohydroxyselenide was obtained, however, the product contained substantial amounts of impurities (TLC) which were not removed after flash chromatography. In contrast, the condensations using the silyl enol ether 62a were very clean as well as efficient.



70 62b, 71% (29)

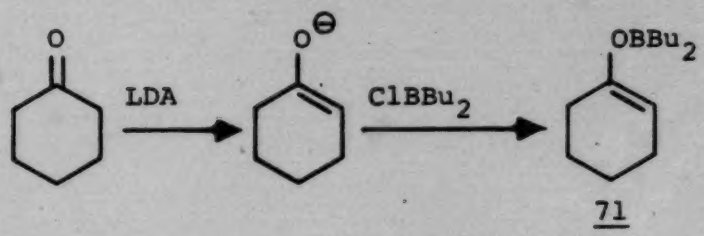
For the enone 67a, 1,4-vinylation was not an efficient process and there was no advantage in trapping the enolate as the silyl enol ether. Therefore the condensation with phenylselenoacetaldehyde was carried out directly. For large ring enones, the yield of 1,4-addition product appears to be dependent on the solvent,[68] with high yields being obtained in solvents of lower polarity

(e.g., ether) and low yields in solvents of higher polarity (e.g., tetrahydrofuran). Unfortunately, the divinylmagnesium cuprate used during this investigation was not soluble in ether, and this necessitated the use of tetrahydrofuran.

The condensations to give 64b, 65b, 68b and 69b were carried out using the zinc enolates of the corresponding ketones. For each example the enolate was prepared by kinetic deprotonation with lithium diisopropylamide and subsequent addition of zinc chloride.

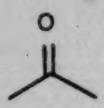
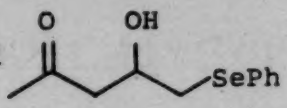
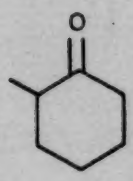
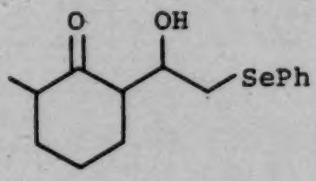
Except for 67b and 68b, the condensations involving the use of zinc enolates showed little stereoselectivity and produced mixtures of both erythro and threo aldol products. That the stereochemistry may actually be subject to a certain amount of experimental control was shown by example 60b. Repetitive condensations of 60a to give 60b usually resulted in a diastereoisomeric mixture of products, however, the ratio of diastereoisomers one obtained varied greatly from run to run. In some instances essentially only one diastereoisomer was formed.

The condensation to give 66b was effected using the enol borinate 71 which was prepared as indicated in equation (30). Other examples involving the use of enol borinates are shown in Table VI . For all of the examples listed in this table mixtures of diastereoisomers were



71 (30)

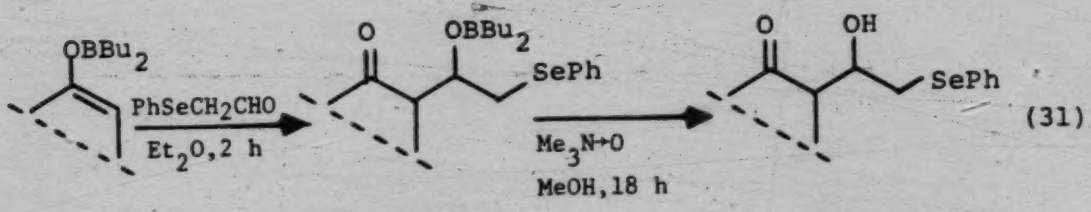
TABLE VI: Condensations via Enol Borinates

STARTING KETONE	CONDENSATION PRODUCT	(%)
72a 	72b 	79[ab]
73a 	73b 	42[bc]
73a	73b + 60b	46[b,d]
66a	66b	78[b,c]

[a]Enol borinate formed using diisopropylethylamine and Bu_2BOTf.[65] [b]Mixture of diastereomers. [c]Enol borinate formed via kinetic deprotonation with LDA and addition of $ClBBu_2$. [d]Enol borinate formed via LDA/$ClBBu_2$ under thermodynamic conditions (i.e., two equivalents of 73a). Ratio of 73b:60b was 1:5.2.

formed and little stereoselectivity was observed. Despite the lack of selectivity, no attempt was made to discover conditions under which selectivity might be attained, since

the erythro/threo configuration of the hydroxyketone is removed during conversion to the olefin. The usual conditions employed after condensation to liberate the hydroxyketone from the resulting oxy-borane (i.e., aqueous hydrogen peroxide) could not be used in our examples since this caused oxidation of the selenium moiety and subsequent product decomposition. Therefore the oxy-borane was oxidatively hydrolyzed using trimethylamine-N-oxide,[69] as shown by the general reaction in equation (31).



(31)

For examples, 61b, 62b and 63b in Table V it was possible to separate the isomeric ketohydroxyselenides and when we examined such isomers individually, we noticed no substantive difference in the ease of generating the double bond (Scheme VIII).[70] Extensive ^{1}H-NMR decoupling of the ketohydroxyselenides and the corresponding olefinic products determined that the relationship of the substituents attached to the ring for 62b, 63b and 67b was trans[71] in each case. While the vinyl and 1-hydroxy-2-(phenylseleno)-ethyl groups for 61b are also likely to be trans, the presence of the angular methyl substituent did not allow the stereochemistry to be readily determined.

Example 69b in Table V demonstrates that phenylselenoacetone[72] can also be condensed with ketone enolate-species to yield the ketohydroxyselenide. The good yield of aldol product obtained for this example demonstrates the potential synthetic utility of phenylselenoacetone with zinc enolates[73] since the condensation product 69b permits the formation of an isopropylene unit which is also an important synthon for the construction of numerous terpenes.[74]

As an extension of this work, condensations were attempted using methylselenoacetaldehyde. Condensations with this aldehyde gave low yields (ca. 30%) of aldol products using either enol borinates or zinc enolates. In view of the yields obtained with phenylselenoacetaldehyde the yields with methylselenoacetaldehyde were judged to be unsatisfactory and the use of this aldehyde was discontinued.

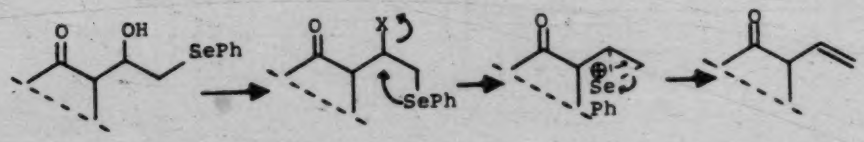
Generation of the Double Bond

As expressed previously, conversion of β-hydroxyselenides into olefins is a known process,[1a] with a variety of procedures reported in the literature. It is because of this that ketohydroxyselenides (55, X = SePh) possess important synthetic potential.

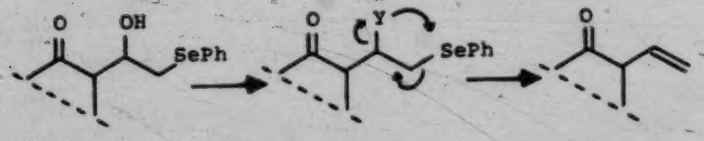
Unfortunately, when the examples in Table V were subjected to the literature procedures for formation of

the desired olefin, none of the methods proved to be useful. Although some methods did result in the formation of the desired olefinic material (TLC control), purification of the product proved to be difficult and often gave low yields of product when purification was finally achieved.

Variations of the literature procedures as well as some potentially new reactions were examined in the hope of finding a suitable procedure. The results of the various attempts are summarized in Table VII . The general theme behind all of the reactions listed in this table is centered on the conversion of the hydroxy functional group into an appropriate leaving group such that elimination can occur, either via an episeleniranium ion which then collapses to the product (eq. (32)), or by a concerted displacement of the selenium moiety (eq. (33)). For most of the



(32)



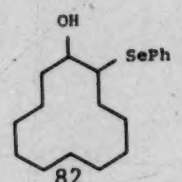
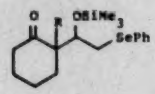
(33)

TABLE VII: OLEFIN FORMATION REACTIONS

REACTION METHOD	HYDROXYSELENIDE	PRESENCE OF SM	PRESENCE OF OLEFIN	YIELD OF OLEFIN[a]	PURITY[b]	CONVENIENCE[c]
1) Et_3N or $(\text{pyridine})_2NEt/SOCl_2/RT$[75]	66b	✓	✓	✓	-	✓
2) $Et_3N/SOCl_2/-20°C$	66b	✓	-	-	-	✓
3) n-BuLi/$SOCl_2$/NaI/HMPA/-30°C→RT	66b	-	-	-	-	✓
4) NaH/o-phenylenephosphorochloridite/RT[75]	66b	-	-	-	-	✓
5) Me_3SiCl/NaI/RT	60b	✓	-	-	-	✓
6) Me_3SiCl/pyd or Et_3N/RT	60b	✓	-	-	-	✓
7) 1-(trimethylsilyl)-1H-imidazole	66b	-	-	-	-	✓
8) Et_3N/CF_3SO_2Cl/RT	66b	✓	-	-	-	✓
9) $Et_3N/MeSO_2Cl/0°C$[76]	60b	✓	-	-	-	✓
10) $Et_3N/MeSO_2Cl$/RT-slow addition	60b	-	✓	✓	✓	✓
11) NaH or t-BuLi/TFAA/NaI/RT[77]	60b	-	-	-	-	✓
12) $PhSeSiMe_3$/NaH/65°C	60b	-	-	-	-	✓
13) Et_3N/1-ethyl-2-fluoropyridium tetrafluoroborate/56°C[78]	60b	✓	✓	-	✓	-
14) pyd./$COCl_2$/NaI	60b	-	✓	✓	✓	✓

continued...

TABLE VII (continued)

15) pyd/$COCl_2$/NaI	$CH_3(CH_2)_9CH(OH)CH_2SePh$ 83	-	✓	✓	✓	✓
16) pyd or 4-N,N-dimethylamino-pyridine/carbonochloridothioic acid-S-phenyl ester	60b	✓	-	-	-	✓
17) NaH/ "	60b	-	-	-	-	✓
18) 4-N,N-dimethylaminopyridine/ carbonochloridothioic acid-O-(3-chlorophenyl)ester	60b	✓	-	-	-	✓
19) " / " / 110°C/2h	 82	-	✓	✓	✓	-
20) NaH/carbonochloridothioic acid-O-(3-chlorophenyl)ester	60b	-	-	-	-	✓
21) $PhSeSiMe_3$/65°C						
	60b' R = Me	✓	-	-	-	✓
	66b' R = H	✓	-	-	-	✓

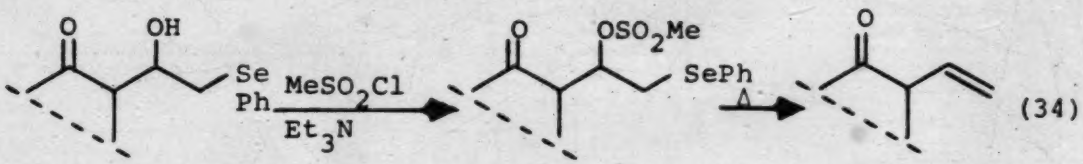
[a]tick indicates a yield over 50%. [b]tick indicates that product could be easily purified. [c]tick indicates that the method was easy to carry out and that the reagents were accessible and/or easy to prepare.

reactions summarized in Table VII no olefinic material was obtained (for many of the reactions large amounts of starting material were detected (TLC control) after work-up). The use of strong bases such as sodium hydride and alkyllithiums resulted in the decomposition of the ketohydroxyselenide without formation of olefinic material. The use of thionyl chloride did result in the formation of olefinic product; however, the material could not be easily purified. The application of silylating reagents to effect elimination was only useful under highly acidic conditions, under neutral or basic conditions only the corresponding silylated product was isolated. Finally, while the use of 1-ethyl-2-fluoropyridinium tetrafluoroborate gave promising results, with a modest amount of olefinic material being formed, the difficulty in preparing and handling this reagent made this method inconvenient to use.

Of the various methods examined, only one was found to be generally useful. It was discovered that if methanesulfonyl chloride was added slowly at room temperature to the ketohydroxyselenide, in the presence of triethylamine, then excellent yields of the olefinic product could be obtained. Although the use of methanesulfonyl chloride and triethylamine had been previously described,[76] use of the conditions reported in the literature did not result in any olefinic product (TLC

control), and most of the starting material was recovered unchanged.

The combination of higher temperature and slower addition was found to be particularly important to obtain optimum yields of the olefin.[79] It appears that the higher temperature is necessary for thermal decomposition of the sulfonate ester 74 to the product (eq. (34)) since, when



(34)

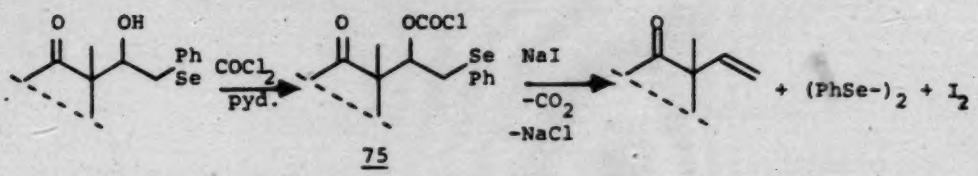
74

similar experiments were carried out at 0°C, large amounts of the methanesulfonate ester could be detected by NMR. Repetitive experiments determined that the slow addition technique was necessary in order to completely convert all of the starting material to the sulfonate ester. This requirement may be due to the intermediacy of a sulfene as the active sulfonating agent in the reaction[80] (generated by the reaction of methanesulfonyl chloride with triethylamine). Such species have been reported to be highly reactive, unstable intermediates,[81] which are capable of reacting with excess methanesulfonyl chloride.[81b] It would appear that the slow rate of addition serves to increase the yield of sulfonate ester by maintaining low concentrations of the sulfene and methanesulfonyl chloride, thus minimizing possible side-reactions which

might cause a depletion of the sulfonating agent.

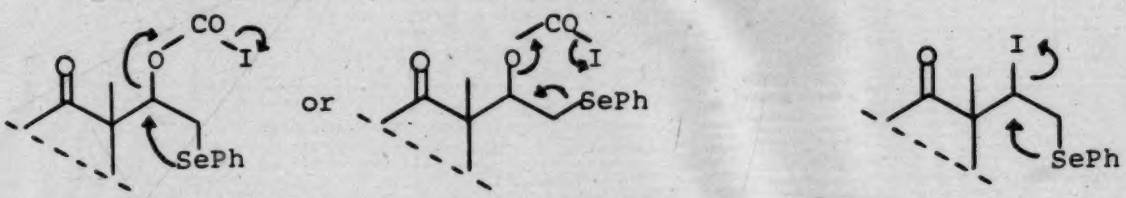
The only other synthetically viable method for effecting elimination to the olefin was that involving treatment of hydroxyselenides with phosgene in the presence of pyridine (in ether solution). Subsequent exposure of the derived chloroformate to sodium iodide in acetonitrile usually resulted in the formation of olefinic product. Unfortunately, of the several cases in which we made a comparison, only 60c and 65c were formed efficiently by this method. It appears that this reaction may only be applicable to substrates which possess angular substituents α to the carbonyl (i.e., 60b, 65b) since substrates possessing hydrogens at that position (i.e., 66b, 69b) yielded only traces of the corresponding olefins.

The mechanism by which the olefin is formed using the phosgene method was not examined, however it is likely that a chloroformate such as 75 is formed initially.[82] While the role that sodium iodide plays during the decomposition to the olefin has not been determined, the presence of iodine in the reaction mixture at the completion of the reaction suggests an oxidation/reduction reaction, possibly involving selenium. It seems plausible that the selenium moiety is being removed from the carbon-skeleton in the form of phenylselenenyl iodide, which decomposes[2] to diphenyldiselenide and iodine (eq. (35)). Prior to product



75 (35)

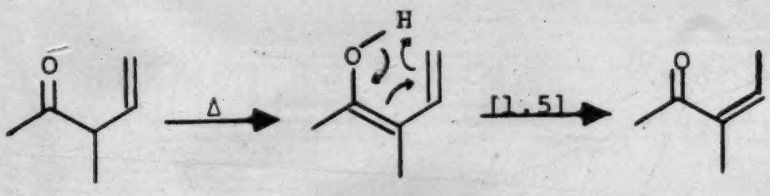
formation the iodide may nucleophilically displace the chlorine atom to give an unstable iodoformate 76,[83] or displace the chloroformate substrate to give an iodoselenide 77 which then collapses to product.



76 77

The results obtained by both the methanesulfonyl chloride and phosgene methods to give the desired olefinic products are summarized in Table V . Although not obvious from the Table, the methanesulfonyl chloride method of elimination always proceeded efficiently, producing high yields of the olefinic products. Spectroscopically determined yields have indicated that the variation in the yield of required olefin is a consequence of the tendency for β, γ-unsaturated ketones to isomerize to the conjugated analogues and is not due to the synthetic method per se. Examples which were particularly sensitive

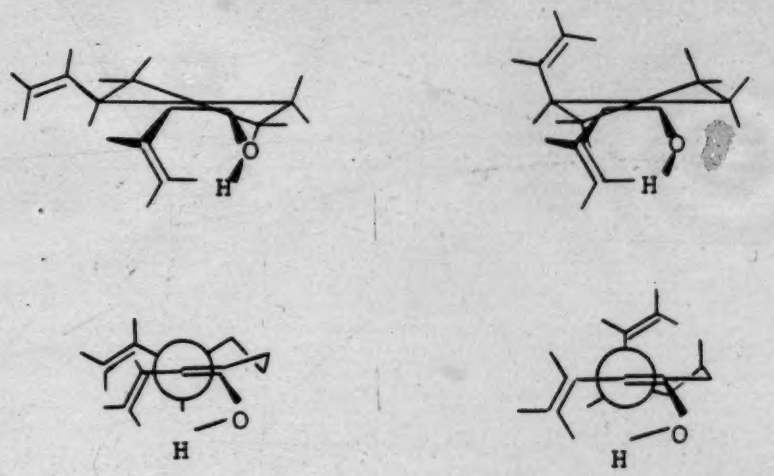
to isomerization were 66c and 68c. It was noted that the sensitivity of such ketones to isomerization appeared to be directly dependent on ring size, with the larger ring ketones being less sensitive.[84] In addition to this observation it was noted that the presence of other substituents on the cyclic ketone (excluding cases where conjugation is blocked) as in 62c, 63c and 67c, appears to discourage isomerization since these examples were less susceptible to rearrangement. Inspection of Dreiding models suggests that the increased stability displayed by these examples may be attributed to steric factors. It is probable that the thermal isomerization of these compounds occurs via a transition state involving a [1,5] sigmatropic rearrangement of the corresponding enol (eq. (36)). If this is correct then the stability displayed



(36)

by 62c, 63c and 67c can be explained by examining the non-bonding interactions which disfavor the formation of the enol for these examples. Shown in Figure I are the two likely conformations for the enol form of 62c. As seen in the diagrams, both conformations have serious

Figure I



non-bonding interactions involving 1,3 diaxial interactions or eclipsing interactions, which are not present in the keto form. The formation of the enol for 67c is similarly disfavored since either eclipsing of the two vinyl pendants results or unavoidable transannular interactions, involving the vinyl substituent on C3, occur.

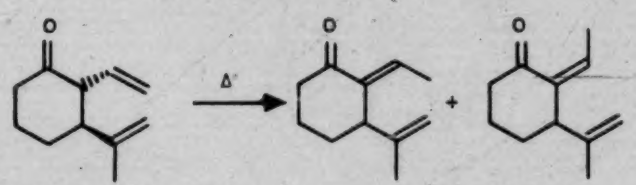
Application to Cope and oxy-Cope Rearrangements

When the diene 67c was heated at 200°C it underwent Cope rearrangement to give 67d in 90% yield after purification (eq.(37)). Proton NMR decoupling of 67d established

(37)

67d

that the configurations about the double bonds in the product were trans, suggesting that rearrangement occurred via a chair-like transition state as shown in equation (37) to give the indicated product.[85] In contrast to this example, the attempted Cope rearrangement of 63c under similar conditions failed to give the ring expanded product and instead gave only products resulting from isomerization to the α,β- unsaturated ketone (eq. (38)). That 67c readily undergoes ring expansion while 63c fails

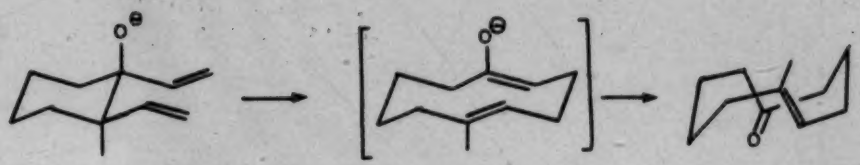


63d 63d' (38)

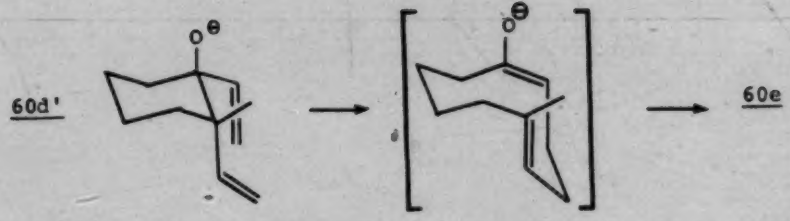
to yield any ring-expanded product whatsoever is presumably a consequence of medium ring transannular interactions. Cope rearrangement of 63c involves expansion of a normal into a medium ring system, while Cope rearrangment of 67c involves the conversion of a medium into a large ring system. For 67c the overall process results in the attendant release of transannular interactions, thus favoring ring expansion. For 63c ring expansion would create transannular interactions thereby making this process less favorable.

When compound 60c was treated with vinylmagnesium bromide two isomers, 60d and 60d' (Scheme IX), were formed.

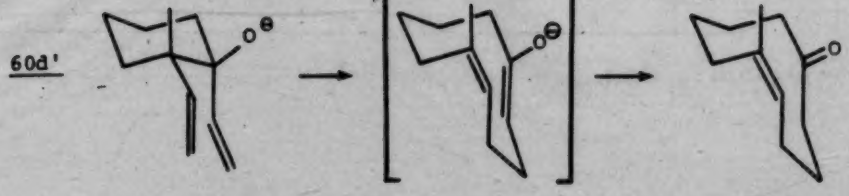
Scheme IX



60d 60e



60d' 60e



60d' 60e'

Separation of the alcohols and oxy-Cope rearrangement of the derived potassium alkoxides in refluxing tetrahydrofuran[52] proved to be a very facile process. Compound 60d gave an 84% yield of 60e without any contamination due to 60e', while the other isomer, 60d', resulted in a 95% yield of ring expanded product consisting of 90% 60e and 10% of 60e'. Assuming chair transition states for the rearrangement, the product distributions can be interpreted as in Scheme IX.[86] As shown, the isomer possessing the pendant vinyl groups trans to one another (60d) is only capable of forming 60e. However, compound 60d' in which the vinyl substituents are cis to one another can rearrange to give either 60e or 60e'. The fact that 60e is the major product formed suggests that the conformation in which the oxygen substituent is axial for 60d' is favored over the alternative in which the methyl group is axial. The product distribution obtained from 60d' closely approximates that expected from the corresponding alcohol in that the difference in free energy between equatorial and axial substituents for hydroxy and methyl groups (0.6-1.5 kcal/mole)[87] suggests a distribution of final products 75-95% in favor of 60e.

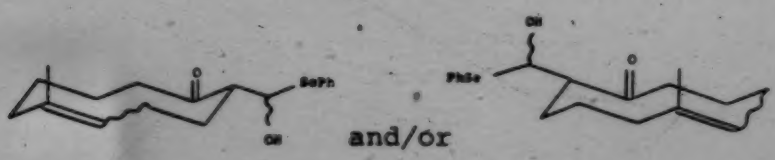
As indicated in Scheme IX the oxy-Cope rearrangement of 60d or 60d' results in the formation of an enolate prior to protonation. In principle such a process is conveniently set up for a second aldol condensation with

phenylselenoacetaldehyde, thus making the overall sequence of reactions a repetitive one.

When a mixture of 60d and 60d' (1:2.1, K^+ counterion) was refluxed in tetrahydrofuran and then condensed with phenylselenoacetaldehyde, as shown in equation (39), a 64% yield of the ring-expanded ketohydroxyselenide was

$$\underline{60d} + \underline{60d'} \xrightarrow[\text{2) } 0°C,\ ZnCl_2 \text{ 3) } 0°C,\ PhSeCH_2CHO \text{ 4) } H^+,\ H_2O]{\text{1) THF, 15 min reflux}} \underline{78} + (\underline{60e} + \underline{60e'}) \quad (39)$$

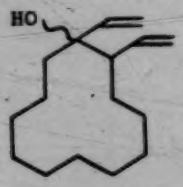
obtained. Despite the acceptable yield from the condensation, the concurrent isolation of 60e and 60e' is synthetically distracting since the enolates indicated in Scheme IX may have been formed in the presence of the protonated analogues, 60e and 60e'. Such a situation allows for enolate equilibration prior to condensation, possibly reducing the regioselectivity of the reaction. Whether such equilibration occurred in the reaction summarized by equation (39) could not be readily determined and the data presently available do not discriminate between the possible regioisomers (i.e., 78 [88]).



and/or

78

In an attempt to prevent enolate equilibration prior to aldol condensation it was necessary to ensure complete deprotonation of the divinyl alcohol prior to oxy-Cope rearrangement. To this effect the alcohol 79[89]



79

was deprotonated at -78°C using potassium diisopropylamide[90] and the alkoxides were then subjected to the same reaction sequence used for the alkoxides 60d and 60d'. An 86% yield of the ring-expanded ketohydroxyselenide 80[91] (eq. (40)) was isolated. The high yield of ketohydroxyselenide obtained for this example is very

(40)

encouraging and the mild conditions of deprotonation (-78°C) and the preparative ease of preparing 80[92] from the alcohol 79 serves to make this an intriguing process from a synthetic viewpoint.

Further studies are currently in progress to accurately determine the regiochemical integrity of 80 and other compounds obtained in a similar fashion.

Conclusion

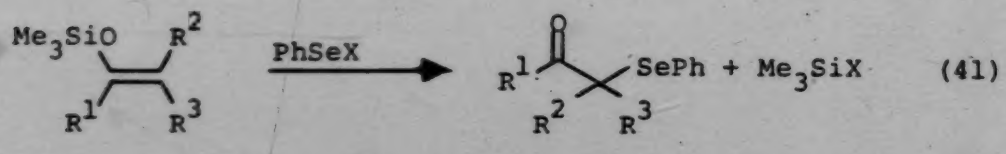
Condensations of enolates with phenylselenoacetaldehyde can be effected to give high yields of the derived aldol condensation products (ketohydroxyselenides). In turn, these products can be efficiently transformed into their β,γ-unsaturated analogues, thereby producing a variety of α-vinylketones, a compound class which, despite its importance, has been relatively inaccessible. The results of these two processes, summarized in Table V , firmly establishes phenylselenoacetaldehyde as a vinyl cation synthon.[93] The potential use of this synthon is displayed by example 63c, which was recently used as an intermediate for tandem Cope-Claisen rearrangements.[53a] Preparation of 63c using more classical methods[53a] involved an otherwise extensive procedure, requiring at least ten synthetic transformations.

In addition to its obvious utility in the synthesis of various mono- and sesquiterpenes, the synthon is adequately suited for ring expansion methodology. While the ring expansion process via Cope rearrangement seems to be limited to examples where the product is not a medium ring, application of the oxy-Cope rearrangement with this synthon appears to be particularly adapted for the synthesis of both medium and large ring compounds.

The recent indications that this synthon may be used to carry out repetitive ring expansions may serve to further expand the utility of this methodology although the regiochemical problems for reactions such as that summarized in equation (40) have not yet been fully investigated.

Methods by which the possibility of enolate equilibration is avoided are currently under investigation. A method which may resolve the problem of regiochemistry is that involving an oxy-Cope rearrangement of a silyl ether to a silyl enol ether.[94] Depicted in Scheme X, this approach would result in a regiochemically pure enolate after cleavage with methyllithium. The ensuing condensation of enolates formed in this fashion has already been demonstrated by examples 60a, 61a, 62a and 63a (Table V) to give high yields of aldol products with phenylselenoacetaldehyde.

Finally, the ability to readily prepare numerous aldehydes and ketones such as 81 using the method developed by Murai[72b] (eq. (41)) provides for additional

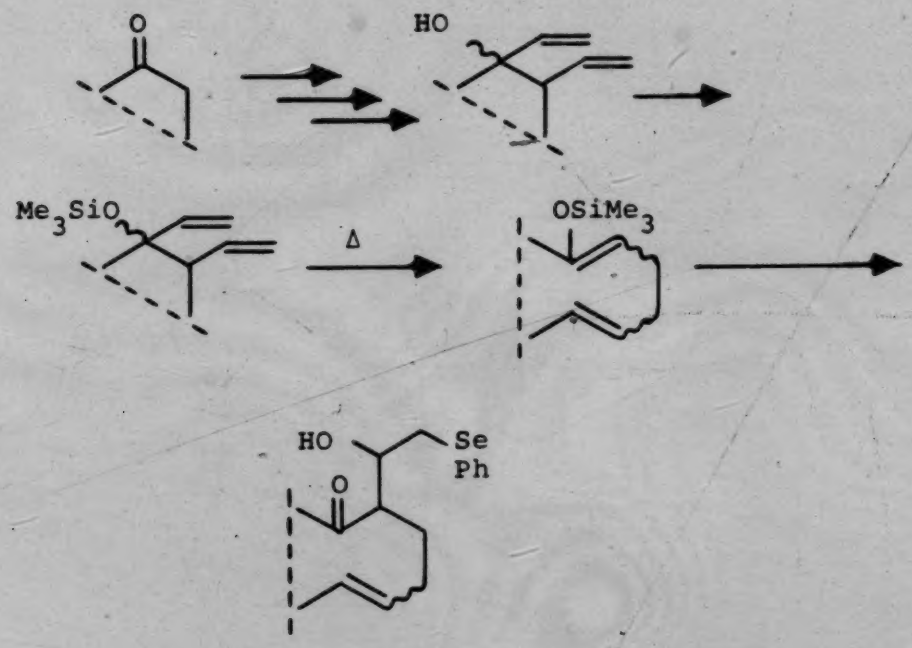


(41)

81

applications of this process in the area of organic synthesis.

Scheme X



The condensation to give 69b followed by conversion to 69c (Table V) is an example of this versatility, with the overall result representing the condensation of an enolate and an isopropenyl cation.

EXPERIMENTAL

Experiments were carried out under nitrogen, purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[95] and through a similar column of Drierite.

Glassware was dried in an oven for at least 3 h (130°C), cooled in a desicator, quickly assembled, and sealed with rubber septa (when applicable). Inlet and exit needles for nitrogen were passed through a septum on the apparatus and nitrogen was purged through the system. The exit needle was removed and the appratus was kept under a slight static pressure of nitrogen (provided no gas was to be generated in the reaction). Materials were quickly weighed into dry flasks which were then sealed with rubber septa and purged with nitrogen. Transfers of moisture- and/or air-sensitive materials were accomplished using dry, well-greased syringes whenever possible (solids were dissolved in a suitable solvent prior to transfer).

Unless stated to the contrary, stirring was effected using a dry, Teflon-coated magnetic stirring bar. Solvents were distilled before use for chromatography or extraction. Dry N,N-diisopropylamine, pentane, hexane, pyridine, Me_3SiCl, Et_3N, MeCN, HMPA, CH_2Cl_2, $CHCl_3$ and DMSO were distilled from CaH_2, dry THF and Et_2O from sodium (benzophenone indicator), dry EtOAc from P_2O_5, and dry

MeOH from magnesium methoxide. U.S.P. absolute EtOH^{96} was used without further drying. Sodium iodide was dried *in vacuo*.

Where necessary, product solutions were dried over anhydrous $MgSO_4$. Solvents were evaporated under water-pump vacuum using a rotary evaporator and a water bath (room temperature). Compounds which were isolated simply by solvent evaporation were subjected to oil-pump evacuation and were checked for consistancy of weight. Melting points were obtained using a Kofler block melting point apparatus. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to oven temperature.

Silica gel used for TLC and PLC was Merck type 60-PF-254. Silica gel used for column chromatography was Merck type 60 (70-230 mesh) and for flash chromatography, Merck type 60 (230-400 mesh). Plates for preparative layer chromatography (60 x 20 x 0.1 cm) were heated for 1 h at 110°C before use. Thin layer chromatography plates were examined under UV radiation (254 nm), treated with iodine vapor and were charred on a hot plate after being sprayed with H_2SO_4 (6 N in methanol).

Vapor phase chromatography was executed using a Hewlett-Packard 5830 A gas chromatograph equipped with an FID detector. Columns used were Hewlett-Packard

prepacked analytical columns. The principal column used for VPC was 6 ft, 10% DEGS, Chromosorb W, 80-100 mesh. Infrared spectra were obtained using a Perkin-Elmer 297 or a Nicolet 7000 FT-IR spectrometer. Proton NMR spectra were obtained using Perkin-Elmer R32, Varian HA 100, Bruker WH-200 and Bruker WH-400 spectrometers using tetramethylsilane as an internal reference. Carbon-13 NMR spectra were acquired using Bruker WP-60, Bruker HFX-90, Bruker WH-100, Bruker WH-200 and Bruker WH-400 spectrometers, using deuterated chloroform as an internal reference. Mass spectra were obtained employing an A.E.I. MS-50 mass spectrometer operating with an ionizing voltage of 70 eV. All V.P.C.—mass spectra determinations were obtained using an AEI MS-12 mass spectrometer in conjunction with a Varian-1400 gas chromatograph. The ionizing voltage of the mass spectrometer was 70 eV and the column used for V.P.C. was a Hewlett-Packard 6 ft, 10% DEGS, Chromosorb W, 80-100 mesh analytical column.

All chiral compounds were obtained as racemates.

Dihydro-5-[(phenylseleno)methyl]-2(3H)-furanone, 6a .[97]

Benzeneselenenyl chloride (955 mg, 4.99 mmol) in EtOAc (12 mL) was added dropwise into a cold (ca. -78°C) solution of 4-pentenoic acid, 6 [98] (500 mg, 4.99 mmol) in EtOAc (10 mL). A further portion of EtOAc (3 mL) was

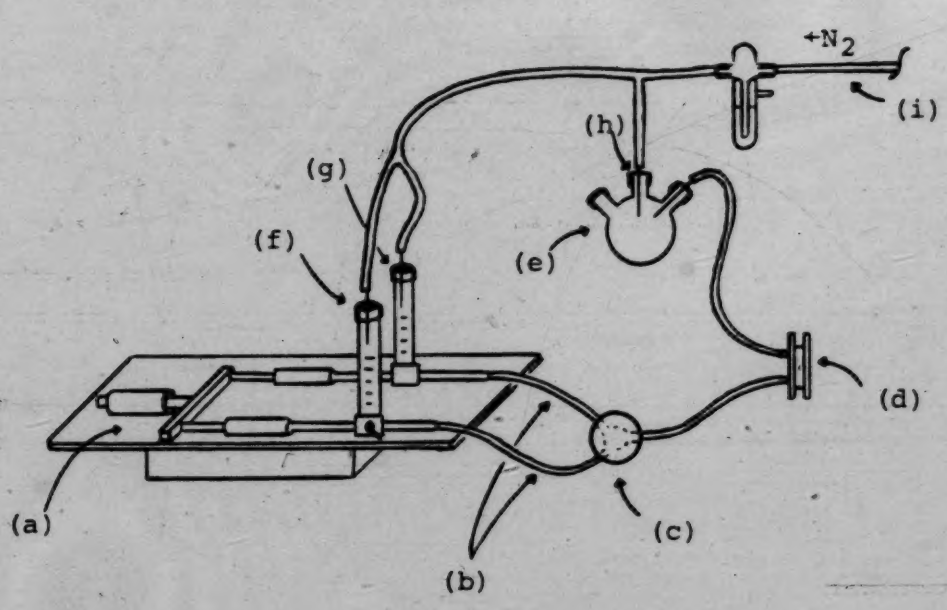
used to rinse residual PhSeCl into the reaction vessel. The cold bath (and hence the mixture) was allowed to attain room temperature. After an overnight period a sample still showed carboxyl absorption (IR). The solution was refluxed 3.5 h to complete formation of 6a (IR control). The solvent was evaporated and the product was isolated by chromatography over silica gel (60 x 2.5 cm) using 1:2 EtOAc—2,2,4-trimethylpentane. Evaporation of the eluate gave 6a (1.20 g, 94%) as a pale yellow, homogeneous (TLC, silica gel, 1:2 EtOAc—2,2,4-trimethylpentane) oil: NMR ($CDCl_3$, 400 MHz) δ 1.88—1.98 (m, centered at 1.93, 1H), 2.32—2.60 (m, 3H), 3.03 (dd, J = 15.2, 9.6 Hz, 1H), 3.26 (dd, J = 15.2, 7.2 Hz, 1H), 4.58—4.72 (m, centered at 4.63, 1H), 7.22—7.32 (m, 3H), 7.48—7.57 (m, 2H); IR (film) 1770 cm^{-1}; exact mass 256.0002 [calcd. for $C_{11}H_{12}O_2{}^{80}Se$, 256.0003]. For analysis a sample was distilled in a Kugelrohr: bp 120°C (0.005 mm). Anal. calcd. for $C_{11}H_{12}O_2Se$: C, 51.78; H, 4.74; O, 12.54. Found: C, 51.88; H, 4.75; O, 12.79.

IR Study on the reaction of PhSeCl with 6.

The study was carried out using a stopped-flow apparatus constructed in the laboratory (Figure II). The apparatus consisted of a conventional dual plunger stopped-flow mechanism (a) which could be operated with manual force. The reagent and substrate solutions were

expelled through teflon tubing (b) into a round teflon disk which served as a mixing chamber (c). An exit tube from this chamber was attached to a 0.05 mm IR solution cell (d). Any excess solution that passed through the IR cell was collected in a reservoir (e) by means of another teflon tube which was attached to the upper port of the cell and terminated with a syringe needle. The needle

Figure II



was inserted into a septum closed flask. The two cylinders on the stopped-flow apparatus were sealed with serum stoppers (f, g) and inlet needles for nitrogen were passed

through these septa as well as the septum (h) on the reservoir. All three nitrogen needles were attached to a common source (i) so as to keep the system under a slight static pressure of nitrogen. Prior to use the entire system was extensively flushed with nitrogen (15 min purge).

A solution of PhSeCl (383 mg, 2.00 mmol) in $CHCl_3$ (5 mL) was placed in one of the stopped-flow cylinders. In the second cylinder was placed a solution of 6 (200 mg, 2.00 mmol) in $CHCl_3$ (5 mL). The stopped-flow plunger was slowly actuated so as to push the solutions through the system and finally into the reservoir (e) thus removing all of the nitrogen in the pathway to the IR solution cell. Final adjustments were made to the IR spectrophotometer and the stopped-flow apparatus was then reset. The apparatus was then actuated in a rapid fashion and the reaction was monitored 1, 2, 6, 11, 16, 21, 31, 44, and 90 min after the time of initial mixing.

Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (intensity constantly decreased); 1742 cm^{-1} (intensity increased and then stopped); 1770 cm^{-1} (intensity constantly increased, obscuring the band at 1742 cm^{-1}). The reaction did not go to completion.

IR Study on the reaction of N,N-diethylbenzeneselenenamide with 6 .

The procedure for the IR study of PhSeCl with 6 was followed using 6 (140 mg, 1.40 mmol) in $CHCl_3$ (3.8 mL) and $PhSeNEt_2$[29] (319 mg, 1.40 mmol) in $CHCl_3$ (3.8 mL). IR spectra were recorded 1, 2, 4, 7 and 18 min after actuation of the stopped-flow apparatus. Two bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (low intensity, constantly decreased); 1760 cm^{-1} (high intensity, constantly increased). The rate of closure to the lactone was extremely fast with respect to the use of PhSeCl.

NMR Study on the reaction of PhSeCl with 6 .

Benzeneselenenyl chloride (383 mg, 2.00 mmol) in $CDCl_3$ (5 mL) and a solution of 6 (200 mg, 2.00 mmol) in $CDCl_3$ (5 mL) were freshly prepared. Using two syringes, a portion (0.35 mL) of each stock solution was placed in a septum sealed NMR tube which had been dried previously and purged with nitrogen. The sample was shaken and quickly placed in the NMR sample probe. NMR spectra of the sample were taken 0.1, 1.3, 3.0, and 9.5 h after mixing.

The rapid appearance of the chloroselenide 24 followed by the slower formation of chloroselenide 25 (at the expense of the former) was observed. Traces

of the starting acid 6 were present up to 3 h after addition as judged by the presence of multiplets at δ 5.05 and δ 5.83. The intensity of the carboxylic acid proton remained close to unity throughout the experiment. Chloroselenide 24 had inter alia: δ ($CDCl_3$, 400 MHz) 3.28 [-C<u>H</u>(SePh)CH_2Cl], 3.60 and 3.89 [-CH(SePh)C<u>H</u>$_2$Cl]. Chloroselenide 25 had inter alia: δ ($CDCl_3$, 400 MHz) 3.12 and 3.37 [-CH(Cl)C<u>H</u>$_2$SePh], 4.08 [-C<u>H</u>(Cl)CH_2SePh].

IR Study on the reaction of $PhSeCl_3$ with 6 .

The procedure for the IR study of PhSeCl and 6 was followed using 6 (38.1 mg, 0.381 mmol) in $CHCl_3$ (7.5 mL) and $PhSeCl_3$[30] (100 mg, 0.381 mmol) in $CHCl_3$ (7.5 mL). IR spectra were recorded 1, 3, 6 and 11 min after actuation of the stopped-flow apparatus. Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (s); 1740 cm^{-1} (m); 1775 cm^{-1} (w). The reaction appeared to stop after initiation. Spectra taken after 1 min were identical.

Reaction of PhSCl with 6 .

Benzenesulfenyl chloride[99] (194 mg, 1.34 mmol) in CCl_4 (4 mL + 1 mL rinse) was added to 6 (101 mg, 1.01 mmol) in CCl_4 (4 mL) at -20°C. The reaction was monitored by withdrawing small aliquots of the mixture and obtaining

a solution IR spectrum. The mixture was allowed to warm to room temperature overnight and another aliquot was withdrawn and examined by IR spectroscopy. Since a large amount of acid was still present, triethylamine (102 mg, 1.01 mmol) was added to the reaction vessel causing complete lactonization (IR control). The mixture was filtered through a column of silica gel (2 x 10 cm), first using CCl_4 as the eluting solvent to remove $(PhS-)_2$ and then CH_2Cl_2 to obtain the lactonic material. Evaporation of the CH_2Cl_2 resulted in an oil: IR (neat) 1775 (s), 1735 cm^{-1} (w). The NMR spectrum of the residue was complex and not amenable to interpretation.

Reaction of PhSCl with sodium 4-pentenoate.

Sodium hydrogen carbonate (258 mg, 3.07 mmol) was added to a solution of 6 (307 mg, 3.07 mmol) in water (3 mL). The solution was stirred overnight and evaporated under high vacuum (0.005 mm Hg) for 3 h to give sodium 4-pentenoate (366 mg) as a light, electrostatic, white solid.

Benzenesulfenyl chloride (145 mg, 1.00 mmol) in CCl_4 (4 mL + 1 mL rinse) was added to sodium 4-pentenoate (122 mg, 1.00 mmol) in CCl_4 (4 mL) at -20°C. The mixture was stirred at -20°C for 1 h. The cold bath was then removed and the mixture was allowed to attain room

temperature while being stirred overnight. Small aliquots were removed at elapsed time intervals of 0.5, 3.5 and 22 h, and were examined by IR spectroscopy. Four bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (s, intensity did not change); 1740 cm^{-1} (m, intensity did not change); 1760 cm^{-1} (w, intensity decreased); 1788 cm^{-1} (m, intensity increased).

Treatment of 6a with HCl.

Gaseous HCl was slowly passed through a solution of 6a (200 mg, 0.784 mmol) in ether (7 mL) for 5 min. The flask was slightly pressurized with HCl gas and stirred for 5 min. Evaporation of the solvent left a residue which contained a carboxylic acid: IR (neat) 1710 cm^{-1}.

(3aα,6α,6aα)-Hexahydro-6-(phenylseleno)-2H-cyclopenta[b]-furan-2-one, 7a .[97]

With the exception noted below the procedure for 6a was followed using 2-cyclopentene-1-acetic acid, 7 [20] (252 mg, 2.01 mmol) in EtOAc (5 mL) and PhSeCl (384 mg, 2.01 mmol) in EtOAc (5 mL + 5 mL rinse). After 24 h at room temperature (i.e., no reflux period) the reaction was complete (IR control). Chromatography over silica gel (60 x 1 cm) using 1:2 EtOAc—2,2,4-trimethylpentane gave 7a (412 mg, 73%) as a homogeneous (TLC, silica gel,

1:2 EtOAc—2,2,4-trimethylpentane) pale yellow oil: NMR ($CDCl_3$, 400 MHz) δ 1.56 (m, 1H), 1.82 (m, 1H), 2.12—2.38 (m incorporating dd at 2.32, J = 19.3, 2.9 Hz, 3H), 2.80 (dd, J = 19.3, 10.4 Hz, 1H), 3.09 (m, 1H), 3.87 (m, 1H), 4.88 (d, J = 6.4 Hz, 1H), 7.20—7.32 (m, 3H), 7.44—7.56 (m, 2H); IR (film) 1773 cm^{-1}; exact mass 282.0148 [calcd. for $C_{13}H_{14}O_2{}^{80}Se$, 282.0159]. Material from another experiment was distilled in a Kugelrohr: bp 135°C (0.001 mm). Anal. calcd. for $C_{13}H_{14}O_2Se$: C, 55.53; H, 5.02; O, 11.38. Found: C, 55.61; H, 5.07; O, 11.39.

IR Study on the reaction of PhSeCl with 7 .

The procedure for the IR study of 6 and PhSeCl was followed using 7 (200 mg, 1.59 mmol) in $CHCl_3$ (5 mL) and PhSeCl (304 mg, 1.59 mmol) in $CHCl_3$ (5 mL). IR spectra were recorded 30 sec, 1, 2, 6, 11, 20, 50 min, 4 h and 24 h after actuation of the stopped-flow apparatus. Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (intensity decreased), 1738 cm^{-1} (intensity increased and then decreased), 1768 cm^{-1} (intensity increased). The reaction did not go to completion.

IR Study on the reaction of 2,4-dinitrobenzeneselenenyl chloride with 7 .

The procedure for the IR study of 6 and PhSeCl was followed using 7 (100 mg, 0.793 mmol) in $CDCl_3$ (5 mL) and 2,4-dinitrobenzeneselenyl chloride[31] (223 mg, 0.793 mmol) in $CDCl_3$ (5 mL). IR spectra were recorded 30 sec, 1, 5, 10, 25, 41, 70 min, 3 and 18 h after actuation of the stopped-flow apparatus. Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (s), 1740 cm^{-1} (m), 1765 cm^{-1} (w). The intensity of the bands did not alter after 70 min.

Reaction of PhSeCl with 21 .[97]

Benzeneselenenyl chloride (191 mg, 0.997 mmol) in THF (2 mL + 1 mL rinse) was added to a stirred suspension of 21 [100] (121 mg, 0.997 mmol) in THF (2 mL) at room temperature. The mixture was stirred overnight and monitored (TLC) periodically for the formation of 7a. None was detected. Filtration of the solution and subsequent evaporation of the solvent from the filtrate resulted in a yellow oil: IR (film) 1772, 1725, 1702 cm^{-1}.

(3aα,7α,7aα)-Hexahydro-7-(phenylseleno)-2(3H)-benzofuranone 8a .[97]

Benzeneselenenyl chloride (764 mg, 3.99 mmol) in EtOAc (10 mL) was added into a solution of 2-cyclohexene-1-acetic acid, 8[101] 500 mg, 3.99 mmol) in EtOAc (10 mL). More EtOAc (5 mL) was used to rinse all the PhSeCl into the reaction vessel. The mixture was refluxed for 7 h, the solvent was evaporated and the residue was partitioned between Et_2O and 5% w/v aqueous $NaHCO_3$. The Et_2O solution was dried and evaporated. Chromatography of the residue over silica gel (60 x 2 cm) using 2:3 EtOAc—2,2,4-trimethylpentane gave, after removal of solvent and Kugelrohr distillation, 8a (975 mg, 82%) as a homogeneous (TLC, silica gel, 1:1 EtOAc—2,2,4-trimethylpentane) oil: bp 125° (0.01 mm). Anal. calcd. for $C_{14}H_{16}O_2Se$: C, 56.96; H, 5.46; O, 10.84. Found: C, 56.86, H, 5.47; O, 10.88. Pure material from another experiment had: NMR ($CDCl_3$, 100 MHz) δ 1.00—2.83 (m, 9H), 3.68 (q, J = 4Hz, 1H), 4.40 (t, J = 4 Hz, 1H), 7.15—7.39 (m, 3H), 7.39—7.65 (m, 2H); IR (CCl_4) 1790 cm^{-1}; exact mass 296.0317 [calcd. for $C_{14}H_{16}O_2{}^{80}Se$, 296.0315].

IR Study on the reaction PhSeCl with 8 .

Benzeneselenenyl chloride (208 mg, 1.09 mmol) in $CHCl_3$ (4 mL + 1 mL rinse) was added to 8 (152 mg,

1.09 mmol) in $CHCl_3$ (5 mL). The reaction was monitored periodically by withdrawing samples and recording the IR spectrum of them. Three bands were observed in the carbonyl region of the IR spectrum: 1709 cm^{-1} (intensity decreased), 1754 cm^{-1} (intensity increased and then decreased), 1775 cm^{-1} (intensity increased).

(3aα,8α,8aα)-Octahydro-8-(phenylseleno)-2-cyclohepta[b]-furan-2-one, 9a.

Benzeneselenenyl chloride (177 mg, 0.924 mmol) in Et_2O (3 mL) was added to a solution of 2-cycloheptene-1-acetic acid, 9[26] (142 mg, 0.924 mmol) in Et_2O (3 mL). Additional Et_2O (3 mL) was used to transfer residual PhSeCl. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed over silica gel (60 x 2 cm) using 1:1 heptane—EtOAc. Evaporation of appropriate fractions afforded 9a (277 mg, 97%) as a viscous, homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) oil: NMR ($CDCl_3$, 400 MHz) δ 1.10—2.34 (m, 9H), 2.40—3.02 (m, incorporating dd at 2.84, J = 16.8, 9.5 Hz, 2H), 3.40 (t, J = 9.5, 8.8 Hz, 1H), 4.60 (dd, J = 10.0, 6.2 Hz, 1H), 7.15—7.36 (m, 3H), 7.42—7.68 (m, 2H); IR (film) 1785 cm^{-1}; exact mass 310.0473 [calcd. for $C_{15}H_{18}O_2{}^{80}Se$, 310.0473]. Anal. calcd. for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.87; O, 10.35. Found: C, 58.16; H, 5.78;

O, 10.51.

Reduction of 9a with Ph_3SnH.

Triphenyltin hydride[102] (344 mg, 0.980 mmol) was added from a syringe in three equal portions at 30 min intervals to a refluxing solution of 9a (202 mg, 0.653 mmol) in toluene (3 mL). Refluxing was continued for 16 h after the last addition. The reaction mixture was applied to a column of silica gel (60 x 2 cm) and chromatography, using 1:1 heptane—EtOAc, gave (3aα,8aα)-octahydro-2H-cyclohepta[b]furan-2-one (82.8 mg, 82%) as a homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) oil: NMR ($CDCl_3$, 100 MHz) δ 1.00—3.04 (m, 13H), 4.65 (m, 1H); IR (film) 1780 cm^{-1}. No trans lactone[26] was obtained.

IR Study on the reaction of PhSeCl with 9.

The procedure for the IR study of 6 and PhSeCl was followed using 9 (100 mg, 0.704 mmol) in $CHCl_3$ (5 mL) and PhSeCl (135 mg, 0.704 mmol) in $CHCl_3$ (5 mL). IR spectra were recorded 30 sec, 1, 2, 5, 10, 14, 20, 51, and 120 min after actuation of the stopped-flow apparatus. Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (intensity decreased), 1770 cm^{-1} (intensity increased and then decreased), 1785 cm^{-1}

(intensity increased). The reaction was not followed to completion.

cis- and trans-Dihydro-4-methyl-5-[(phenylseleno)methyl]-2(3H)-furanone, 10a.

The method for 9a was followed using 3-methyl-4-pentenoic acid, 10[103] (500 mg, 4.38 mmol) in Et_2O (6 mL) and PhSeCl (839 mg, 4.38 mmol) in Et_2O (7 mL + 7 mL rinse). After a reaction period of 60 h chromatography over silica gel (60 x 3 cm) using 1:1 heptane—EtOAc gave 10a (821 mg, 69%) as a homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) oil: NMR ($CDCl_3$, 200 MHz) δ 1.01 (d, J = 8.4, 1.5H), 1.13 (d, J = 7.2 Hz, 1.5H), 2.12—2.58 (m, 1.5H), 2.62—2.84 (m, 1.5H), 2.90—3.32 (m, 2H), 4.24 (q, J = 6.0 Hz, 0.5H), 4.54—4.68 (m, 0.5H), 7.20—7.36 (m, 3H), 7.48—7.63 (m, 2H); IR (film) 1775 cm^{-1}; exact mass 270.0169 [calcd. for $C_{12}H_{14}O_2{}^{80}Se$, 270.0159]. Anal. calcd. for $C_{12}H_{14}O_2Se$: C, 53.54; H, 5.24; O, 11.89. Found: C, 53.57; H, 5.26; O, 11.93.

The progress of a reaction similar to the one above was monitored using IR spectroscopy. Small aliquots of the mixture were removed 15, 50 min, 11, 40, 48 and 58 h after initiation of the reaction. The solvent was evaporated and a solution (CCl_4) IR was obtained for each aliquot. Three bands were observed in the carbonyl region

of the IR spectrum: 1710 cm^{-1} (intensity decreased), 1735 cm^{-1} (constant, weak intensity), 1788 cm^{-1} (intensity increased). The reaction did not go to completion.

Dihydro-5-methyl-5-[(phenylseleno)methyl]-2(3H)-furanone, 11a and Dihydro-5,5-dimethyl-4-(phenylseleno)-2(3H)-furanone, 12a.

The method for 9a was followed using 4-methyl-4-pentenoic acid, 11[104,105] (150 mg, 1.32 mmol) in Et_2O (3 mL) and PhSeCl (252 mg, 1.32 mmol) in Et_2O (3 mL + 3 mL rinse). After a reaction period of 17 h chromatography over silica gel (60 x 2 cm) using 1:1 heptane—EtOAc gave two lactones as homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) oils: 11a [301 mg, 85% (95% after correction for presence of 12 in the starting material)] and 12a (38 mg, 10%). 11a : NMR ($CDCl_3$, 100 MHz) δ 1.47 (s, 3H), 1.81—2.70 (m, 4H), 3.16 (s, 2H), 7.14—7.32 (m, 3H), 7.42—7.64 (m, 2H); IR (film) 1775 cm^{-1}; exact mass 270.0156 [calcd. for $C_{12}H_{14}O_2{}^{80}Se$, 270.0159]. Anal. calcd. for $C_{12}H_{14}O_2Se$: C, 53.34; H, 5.22; O, 11.84. Found: C, 53.43; H, 5.21; O, 12.08. 12a: NMR ($CDCl_3$, 100 MHz) δ 1.45 (s, 3H), 1.49 (s, 3H), 2.58—3.10 (m, centered at 2.85, 2H), 3.59—3.78 (m, centered at 3.68, 1H), 7.22—7.40 (m, 3H), 7.47—7.70 (m, 2H); IR (film) 1775 cm^{-1}; exact mass 270.0153 [calcd. for $C_{12}H_{14}O_2{}^{80}Se$, 270.0159].

IR Study on the reaction of PhSeCl with 11.[105]

The procedure for the IR study of 6 and PhSeCl was followed using 11 (100 mg, 0.877 mmol) in $CHCl_3$ (5 mL) and PhSeCl (168 mg, 0.877 mmol) in $CHCl_3$ (5 mL). IR spectra were recorded 30 sec, 1, 4, 7, 11, 21 and 25 min after actuation of the stopped-flow apparatus. Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (intensity decreased); 1753 cm^{-1}, this band was replaced by one at 1766 cm^{-1} (overall intensity increased).

(1α,4β,5α)-4-(Phenylseleno)-6-oxabicyclo[3.2.2]non-7-one 13a.

The method for 9a was followed using 4-cycloheptene-1-carboxylic acid, 13[106] (250 mg, 1.78 mmol) in Et_2O (3 mL) and PhSeCl (342 mg, 1.78 mmol) in Et_2O (3 mL + 3 mL rinse). After a reaction period of 24 h chromatography over silica gel (60 x 2 cm) using 1:1 heptane—EtOAc gave 13a (400.0 mg, 76%) as a homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) oil: NMR ($CDCl_3$, 100 MHz) δ 1.56—2.40 (m, 8H), 2.66—2.88 (m, 1H), 3.42—3.70 (m, 1H), 4.56 (broad d, J = 4.6 Hz, 1H), 7.16—7.36 (m, 3H), 7.40—7.64 (m, 2H); IR (film) 1742 cm^{-1}; exact mass 296.0320 [calcd. for $C_{14}H_{16}O_2{}^{80}Se$, 296.0315].

1α,5β,6α)-5-(Phenylseleno)-7-oxabicyclo[4.2.2]decan-8-one, 14a and 1α,4β,5α)-4-(phenylseleno)-6-oxabicyclo[3.3.2]decan-7-one, 14b.

The method for 9a was followed using 4-cyclooctene-1-carboxylic acid, 14[107] (127 mg, 0.825 mmol) in Et_2O (3 mL) and PhSeCl (158 mg, 0.825 mmol) in Et_2O (3 mL + 3 mL rinse). After a reaction period of 17 h chromatography over silica gel (60 x 2 cm) using 1:1 heptane—EtOAc gave a mixture of 14a and 14b (223 mg, 88%) in a ratio of 80:20 (NMR) respectively. Enriched, crystalline samples of 14a and 14b, each containing not more than 15% of the other isomer, were obtained by PLC over silica gel using 1:1 heptane—EtOAc. 14a: mp 51—56°C; NMR ($CDCl_3$, 200 MHz) δ 1.44—2.44 (m, 10H), 2.92—3.07 (m, 1H), 3.74 (dt, J = 11.1, 4.08 Hz, 1H), 4.72—4.86 (m, 1H), 7.24—7.34 (m, 3H), 7.46—7.60 (m, 2H); IR ($CHCl_3$) 1722 cm^{-1}; exact mass 310.0476 [calcd. for $C_{15}H_{18}O_2{}^{80}Se$, 310.0472]. 14b: mp 35—48°C; NMR ($CDCl_3$, 200 MHz) δ 1.44—2.34 (m, 10H), 3.12—3.26 (m, 1H), 3.50—3.72 (m, 1H), 4.53 (dt, J = 7.5, 3.1, 2.5 Hz, 1H), 7.20—7.36 (m, 3H), 7.44—7.59 (m, 2H); IR ($CHCl_3$) 1715 cm^{-1}; exact mass 310.0476 [calcd. for $C_{15}H_{18}O_2{}^{80}Se$, 310.0472]. A mixture of 14a and 14b was used for combustion analysis: Calcd. for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.87; O, 10.35. Found: C, 58.28; H, 5.84; O, 10.27.

3-endo-Hydroxy-2-exo-(phenylseleno)-5-endo-carboxybicyclo-[2.2.2]octane lactone, 15a.

The method for 9a was followed using bicyclo[2.2.2]oct-5-ene-2-endo-carboxylic acid, 15[108] (152 mg, 1.00 mmol) in Et_2O (3 mL) and PhSeCl (211 mg, 1.10 mmol) in Et_2O (3 mL + 3 mL rinse). After 18 h the solvent was evaporated from the resulting suspension and the residue was crystallized twice from cyclohexane to obtain 15a (234 mg, 76%) as a pure (TLC, silica gel, 3:2 heptane—EtOAc), crystalline compound: mp 114—115°C; NMR ($CDCl_3$, 100 MHz) δ 1.10—2.80 (m, 9H), 3.54—3.68 (m, 1H), 4.56—4.74 (m, 1H), 7.18—7.75 (m, 5H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 15.3, 22.0, 28.9, 29.3, 34.7, 36.5, 45.5, 83.2, 127.6, 128.7, 129.5, 133.0, 180.1 ppm; IR (CH_2Cl_2) 1775 cm^{-1}; exact mass 308.0316 [calcd. for $C_{15}H_{16}O_2{}^{80}Se$, 308.0316]. Anal. calcd. for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25; O, 10.41. Found: C, 58.76; H, 5.27; O, 10.35.

Reduction of 15a with Ph_3SnH[109]

Triphenyltin hydride (380 mg, 0.900 mmol) was added to a refluxing solution of 15a (183 mg, 0.600 mmol) in toluene (2 mL). Refluxing was continued for 6 h and the cooled reaction mixture was applied to a column of silica gel (60 x 1 cm). Chromatography, using 3:2 hexane—EtOAc

followed by sublimation (100°C, 0.005 mm) gave 6-*endo*-hydroxybicyclo[2.2.2]octan-2-*endo*-carboxylic acid lactone (64.8 mg, 70%): mp 203—204°C [lit.[110] mp 205—206°C]; NMR ($CDCl_3$, 100 MHz) δ 1.38—2.12 (m, 9H), 2.38—2.78 (m, 2H), 4.56—4.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 15.7, 23.6, 26.1, 27.7, 33.3, 34.4, 37.4, 78.5, 181.3 ppm; IR (CH_2Cl_2) 1770 cm^{-1}; exact mass 152.0833 [calcd. for $C_9H_{12}O_2$, 152.0835].

IR Study on the reaction of PhSeCl with 15 .

The procedure for the IR study of 6 and PhSeCl was followed using 15 (100 mg, 0.658 mmol) in $CHCl_3$ (5 mL) and PhSeCl (126 mg, 0.658 mmol) in $CHCl_3$ (5 mL). IR spectra were recorded 15, 30 and 60 sec after actuation of the stopped-flow apparatus. Due to the high rate of reaction only one band was observed in the carbonyl region of the IR spectrum: 1770 cm^{-1}.

3,4-Dihydro-3-phenyl-4-(phenylseleno)-1*H*-2-benzopyran-1-one, 34a and 1,3-Dihydro-1-[phenyl(phenylseleno)methyl]isobenzofuran, 34b.

The method for 9a was followed using *trans*-stilbene-2-carboxylic acid, 34[111] (200 mg, 0.840 mmol) in Et_2O (3 mL) and PhSeCl (161 mg, 0.840 mmol) in Et_2O (3 mL + 3 mL

rinse). After a reaction period of 18 h chromatography over silica gel (60 x 2 cm), using 5:1 heptane—EtOAc, gave a mixture of 34a and 34b (285 mg, 89%) in a 40:60 ratio (NMR). Enriched, crystalline samples of 34a and 34b, each containing not more than 5% (NMR) of the other isomer were obtained by PLC over silica gel using 5:1 heptane—EtOAc. 34a : mp 121—126°C; NMR ($CDCl_3$, 200 MHz) δ 4.86 (d, J = 2.4 Hz, 1H), 5.85 (d, J = 2.4 Hz, 1H), 6.98—7.78 (m, 13H), 8.05 (m, 1H); IR (CCl_4) 1738 cm^{-1}; exact mass 380.0317 [calcd. for $C_{21}H_{16}O_2{}^{80}Se$, 380.0316]. 34b: mp 120—127°C; NMR ($CDCl_3$, 200 MHz) 4.65 (d, J = 4.4 Hz, 1H), 5.87 (d, J = 4.4 Hz, 1H), 7.02—7.81 (m, 14H); IR (CCl_4) 1780 cm^{-1}; exact mass 380.0315 [calcd. for $C_{21}H_{16}O_2{}^{80}Se$, 380.0315].

Reduction of 34a with Ph_3SnH.

Triphenyltin hydride (265 mg, 0.75 mmol) was added to a refluxing solution of 34a (190 mg, 0.500 mmol) in toluene (3 mL). After 45 min (TLC control) the solvent was evaporated and chromatography over silica gel (60 x 1 cm) using 7:3 heptane—EtOAc gave 3,4-dihydro-3-phenyl-1H-2-benzopyran-1-one (90.0 mg, 80%) as a white, crystalline compound: mp 89—90°C; NMR ($CDCl_3$, 200 MHz) δ 3.06—3.46 (m, 2H), 5.57 (dd, J = 12.4, 4.4 Hz, 1H), 7.24—7.64 (m, 13H), 8.16 (m, 1H); IR (CCl_4) 1735 cm^{-1}; exact mass

224.0837 [calcd. for $C_{15}H_{12}O_2$, 224.0837]. The material was identical to an authentic sample.[112]

Reaction of PhSeCl with 34 , with nitrogen purge.

trans-Stilbene-2-carboxylic acid, 34 (166 mg, 0.741 mmol) was placed in a round-bottomed flask and CCl_4 (4 mL) was added. The solution was purged with nitrogen for 5 min using a needle which passed below the surface of the liquid. In order to minimize solvent evaporation the nitrogen was bubbled through dry CCl_4 before it entered the reaction flask. A solution of PhSeCl (142 mg, 0.741 mmol) in CCl_4 (4 mL + 1 mL rinse) was added and purging of the mixture with nitrogen was continued. Small aliquots were removed from the mixture periodically and examined by IR spectroscopy. Observation of the spectra indicated rapid lactonization to the δ-lactone, 34a (1738 cm^{-1}) with very little formation of the γ-lactone, 34b (1780 cm^{-1}). Eight days after mixing, the product distribution still favored the δ-lactone, 34a (δ-lactone/γ-lactone ratio was 3:1, NMR).

In a similar experiment trans-stilbene-2-carboxylic acid was treated with PhSeCl and CCl_4 without a nitrogen gas purge. IR spectra taken of the mixture at periodical intervals indicated the rapid formation of δ-lactone, 34a which then rearranged substantially to the γ-lactone, 34b.

NMR Study on the reaction of PhSeCl with 34 .

The procedure for the NMR study of 6 with PhSeCl was followed using 34 (333 mg, 1.48 mmol) in $CDCl_3$ (5 mL) and PhSeCl (284 mg, 1.48 mmol) in $CDCl_3$ (5 mL). NMR spectra of the reaction sample were taken 4, 5, 10, 15, 20, 35 min, 2, 4 and 6 h after mixing. Closure of the acid to lactone 34a was observed to be very rapid (inter alia, δ 4.86 and δ 5.85). The signals from this lactone were replaced at a slower rate by those due to lactone 34b (inter alia, δ 4.65 and δ 4.87). The formation of 34b was not evident until 15 min after commencement of the reaction.

3,4-Dihydro-3-phenyl-4-(phenylseleno)-1H-2-benzopyran-1-one, 35a and 1,3-Dihydro-1-[phenyl(phenylseleno)methyl]isobenzofuran, 35b.

The method for 9a was followed using cis-stilbene-2-carboxylic acid, 35[113] (199 mg, 0.888 mmol) in Et_2O (3 mL) and PhSeCl (170 mg, 0.888 mmol) in Et_2O (3 mL + 3 mL rinse). After a reaction period of 48 h chromatography over silica gel (60 x 2 cm) using 5:1 heptane—EtOAc gave a mixture of 35a and 35b (267 mg, 79%) in a 75:25 ratio (NMR): mp 99—116°C; NMR ($CDCl_3$, 200 MHz) δ 4.60 (d, J = 5.1 Hz, 0.25 H), 4.68 (d, J = 2.7 Hz, 0.75H), 5.86 (m,

1H), 6.85—7.65 (m, 13H), 7.85 (m, 0.25H), 8.03 (m, 0.75H); IR (CCl_4) 1740 cm^{-1} (major), 1779 cm^{-1} (minor); exact mass 380.0319 (calcd. for $C_{21}H_{16}O_2{}^{80}Se$, 380.0316].

4b,10b-Dihydro[2]benzopyrano[4,3-c][2]benzopyran-6,12-dione, 36a .

Benzeneselenenyl chloride (237 mg, 1.24 mmol) in DMSO (2 mL + 1 mL rinse) was added to a stirred solution of trans-stilbene-2,2'-dicarboxylic acid[114,115] (276 mg, 1.03 mmol) in DMSO (2 mL) at room temperature. After a reaction period of 22 h the solvent was evaporated (oil-pump vacuum, room temperature, 5 h) and the residue was dissolved in EtOAc (10 mL). A white solid precipitated out of solution and was placed in a flask containing EtOAc (10 mL). The solvent was then refluxed (5 min) and subsequently cooled. Collection of the solid gave 36a[116] (240 mg, 87%): mp (changed crystal form at 240—255°C, began to sublime at 301°C; melted at 325—328°C under rapid heating); IR (KBr) 1724 cm^{-1}; NMR (d_6-DMSO, 200 MHz) δ 6.02 (s, 2H), 7.62—7.88 (m, 6H), 7.98—8.10 (m, 2H); exact mass, m/e 266.0579 (calcd. for $C_{16}H_{10}O_4$, m/e 266.0579). Anal. calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 71.86; H, 3.80.

3aα,6aα)-Hexahydro-3a-(phenylseleno)-2H-cyclopenta[b]furan-2-one, 16a.

Benzeneselenenyl chloride (192 mg, 1.00 mmol) in CH_2Cl_2 (3 mL) was added over 3 min into a stirred solution of 1-cyclopentene-1-acetic acid, 16[117] (126 mg, 1.00 mmol) in CH_2Cl_2 (3 mL). More CH_2Cl_2 (1 mL) was used to rinse the residual contents of the syringe into the reaction vessel. After 16 h the reaction was worked up although it was still incomplete (IR control). The solvent was evaporated and 16a was isolated by chromatography over silica gel (60 x 1 cm) using $CHCl_3$. Removal of the solvent gave 16a (94.0 mg, 33%) as a homogeneous (TLC, silica gel, $CHCl_3$) oil: NMR ($CDCl_3$, 100 MHz) δ 1.45—2.22 (m, 6H), 2.57—3.02 (dd, J = 18.5, 2.8 Hz, 2H), 4.9 (t, J = 3.5 Hz, 1H), 7.18—7.48 (m, 3H), 7.48—7.79 (m, 2H); IR (film) 1770 cm^{-1}; exact mass 282.0151 [calcd. for $C_{13}H_{14}O_2{}^{80}Se$, 282.0159]. Anal. calcd. for $C_{13}H_{14}O_2Se$: C, 55.53; H, 5.02; O, 11.38. Found: C, 55.64; H, 5.02; O, 11.26.

IR Study on the reaction of PhSeCl with 16.

The procedure for the IR study of 6 and PhSeCl was followed using 16 (100 mg, 0.793 mmol) in CH_2Cl_2 (5 mL) and PhSeCl (152 mg, 0.793 mmol) in CH_2Cl_2 (5 mL). IR spectra

were recorded 30 sec, 1, 3, 5, 15 and 45 min after actuation of the stopped-flow apparatus. Three bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (intensity decreased), 1743 cm^{-1} (intensity was constant), 1765 cm^{-1} (intensity increased). Monomeric acid appeared to be present in the mixture (3500 cm^{-1}) and may be responsible for the band at 1743 cm^{-1}. The reaction was not followed to completion.

IR Study on the reaction of PhSeCl with 23 .

The procedure for the IR study of 6 and PhSeCl was followed using 23[22c] (200 mg, 1.43 mmol) in CH_2Cl_2 (10 mL) and PhSeCl (273 mg, 1.43 mmol) in CH_2Cl_2 (10 mL). IR spectra were recorded 1, 2, 4, 9, 12, 17, 22 min and 20 h after actuation of the stopped-flow apparatus. Four bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (intensity decreased), 1752 cm^{-1} (intensity was constant), 1772 cm^{-1} which was later obscured by a band at 1782 cm^{-1} (intensity increased). Monomeric acid appeared to be present in the mixture (3500 cm^{-1}) and may be responsible for the band at 1752 cm^{-1}. The reaction did not go to completion.

5-(Phenylseleno)-tetrahydropyran-2-one, 41.

Ozone was passed through a cold (ca. -78°C) solution of 1-methoxycyclopentene[118] (12.8 g, 130 mmol) in MeOH

(190 mL) until the solution became blue. The excess of ozone was removed by a stream of nitrogen and Me_2S (16.2 g, 260 mmol) was added dropwise to the cold solution. The cooling bath was removed and the mixture was left overnight. Evaporation of the solvent gave a residue which was dissolved in CH_2Cl_2 (150 mL). The solution was washed with water (3 x 50 mL), dried (Na_2SO_4), and evaporated. Distillation using a spinning band apparatus gave 37 (4.79 g, 34%) as a pure (VPC) liquid: NMR ($CDCl_3$, 60 MHz) δ 1.58—2.72 (m, 6H), 3.63 (s, 3H), 9.75 (t, J = 1.4 Hz, 1H); IR (film) 2820, 2720, 1735 and 1720 cm^{-1}.

To a solution of 37 (3.25 g, 25.0 mmol) in EtOAc (100 mL) was added PhSeCl (5.79 g, 30.0 mmol) in EtOAc (120 mL).[72a] Concentrated HCl (2 drops) was added and the mixture was stirred for 17 h. The solvent was evaporated and the yellow residue was chromatographed over silica gel (60 x 2.5 cm) using 1:1 heptane—EtOAc to give 38 (1.93 g, 22%) as a homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) liquid: IR (film) 3060, 2820, 2720, 1730 and 1700 cm^{-1}.

Sodium borohydride (600 mg, 15.9 mmol) was added in portions to a stirred solution of 38 (1.10 g, 13.9 mmol) in MeOH (15 mL). Fifteen min after the last addition the mixture was poured into saturated aqueous $NaHCO_3$

(15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was dried (Na_2SO_4) and evaporated. Chromatography of the residue over silica gel (60 x 1 cm) using 1:1 heptane—EtOAc gave 39 (580 mg, 52%) as a pure (TLC, silica gel, 1:1 heptane—EtOAc) liquid: NMR ($CDCl_3$, 100 MHz) δ 1.62—3.82 [m (including a sharp singlet at 3.67), 11H], 7.15—7.40 (m, 3H), 7.42—7.72 (m, 2H); IR (film) 3450, 1732 cm^{-1}; exact mass 288.0264 [calcd. for $C_{12}H_{16}O_3{}^{80}Se$, 288.0265].

The methyl ester 39 (213 mg, 0.740 mmol) was converted into the hydrazide 40 by the addition of 85% w/w $NH_2NH_2 \cdot H_2O$ (180 mg) in MeOH (2 mL). After stirring the reaction mixture for 40 h (TLC control) the solvent was evaporated to afford 40 (178 mg, 83%) as a pale yellow oil: NMR ($CDCl_3$, 100 MHz) δ 1.64—2.52 (m, 4H), 2.92—4.06 (m, 7H), 7.16—7.65 (m, 5H); IR (film) 3400, 1640 cm^{-1} (broad); exact mass 288.0386 [calcd. for $C_{11}H_{16}N_2O_2{}^{80}Se$, 288.0377].

A solution of 40 (70.0 mg, 0.240 mmol) in CH_2Cl_2 (2 mL) was added slowly from a syringe to a stirred suspension of $PhSeO_2H$[119] (94.0 mg, 0.500 mmol) in CH_2Cl_2 (1 mL). The rate of addition was controlled so as to maintain a steady rate of nitrogen evolution. When nitrogen evolution had ceased the mixture was stirred for an additional 30 min. The solvent was evaporated

and the residual yellow oil was chromatographed over silica gel (30 x 1 cm) using 1:1 heptane—EtOAc to give compound 41 (33.0 mg, 54%) as a yellow, homogeneous (TLC, silica gel, 1:1 heptane—EtOAc) oil: NMR ($CDCl_3$, 200 MHz) δ 1.80—2.08 (m, 1H), 2.20—2.42 (m, 1H), 2.46—2.80 (2H), 3.50 (heptet, J = 4.9 Hz, 1H), 4.25 (dd, J = 11.6, 9.6 Hz, 1H), 4.47 (qd, J = 11.6, 4.8, 1.8 Hz, 1H), 7.22—7.48 (m, 3H), 7.52—7.72 (m, 2H); IR ($CHCl_3$) 1735 cm^{-1}; exact mass 255.9994 [calcd. for $C_{11}H_{12}O_2{}^{80}Se$, 256.0002].

Exchange reaction between 2-chloro-3-(phenylseleno)butane and cyclopentene.

Three solutions (#1, #2, #3) of PhSeCl (316 mg, 1.65 mmol) in Et_2O (10 mL) were prepared. Into each solution trans-2-butene was bubbled at a modest rate for approximately 6 min. (Three min after the start of the gas flow the solutions changed color, becoming light yellow from a deep orange). Using a syringe, neat cyclopentene (1.12 g, 16.5 mmol) was injected into each flask. Acetic acid (99.1 mg, 1.65 mmol) was added to solution #1 and dry HCl gas was bubbled for 10 sec through solution #2. Solution #3 was left as a control. All three samples were stirred overnight at room temperature.

The residual acetic acid in solution #1 was converted to methyl acetate with diazomethane and aliquots from each

solution were removed and the volatile components evaporated. An NMR spectrum was obtained for each residue.[120]

Solution #1 underwent 37% exchange, solution #2 underwent 12% exchange and solution #3 underwent 6% exchange. For solution #1 the formation of 2-acetoxy-3-(phenylseleno)butane and trans-1-acetoxy-2-(phenylseleno)-cyclopentane were also observed.[33a]

In a similar experiment using CCl_4 as the solvent instead of Et_2O no exchange was observed.

Exchange reaction between trans-1-chloro-2-(phenylseleno)-cyclopentane and 2-cyclopentene-1-acetic acid.

Benzeneselenenyl chloride (150 mg, 0.783 mmol) in Et_2O (5 mL) was added dropwise from a syringe to a solution of cyclopentene (107 mg, 1.57 mmol) in Et_2O (5 mL). The resulting faintly colored mixture was stirred for 30 min at room temperature and then 2-cyclopentene-1-acetic acid (98.8 mg, 0.783 mmol) in Et_2O (5 mL) was added. After a further period of 17 h the solvent was evaporated and the residue was chromatographed over silica gel (60 x 2 cm) using 5:1 heptane—EtOAc to afford a mixture (146 mg) of trans-1-hydroxy-2-(phenylseleno)cyclopentane [formed by hydrolysis of trans-1-chloro-2-(phenylseleno)cyclopentane] and 7a in a 60:40 ratio (NMR). The mixture had: NMR ($CDCl_3$, 100 MHz) δ 1.20—2.40 (m, 5.8 H), 2.60—3.24 (m, including a q centered at 2.81, J = 18.3, 10.6 Hz, 1.2H),

3.38 (m, 0.4H), 3.87 (m, 0.6H), 4.12 (m, 0.4H), 4.88 (d, J = 6.3, 0.6H); IR (film) 3460, 1772 cm^{-1}.

Exchange reaction between the chloroselenide of 6 and 7.

Benzeneselenenyl chloride (239 mg, 1.25 mmol) in Et_2O (4 mL + 1 mL rinse) was added to 6 (150 mg, 1.50 mmol) in Et_2O (4 mL) at room temperature. The mixture was stirred for 75 min and 7 (189 mg, 1.50 mmol) in Et_2O (3 mL + 1 mL rinse) was added. The solution was stirred overnight and examined by TLC. Inspection of the plate revealed a large amount of lactone 6a and only a trace of lactone 7a.

NMR Study on the reaction of PhSeCl with methyl 4-pentenoate.

The procedure for the NMR study of 6 with PhSeCl was followed using methyl 4-pentenoate[121] (150 mg, 1.31 mmol) in $CDCl_3$ (5 mL) and PhSeCl (252 mg, 1.31 mmol) in $CDCl_3$ (5 mL). NMR spectra of the reaction sample were taken 1, 5, 60, 90 and 150 min after mixing.

The rapid appearance of the chloroselenide 24'[122] followed by the slower formation of chloroselenide 25' (at the expense of the former) was observed. The double bond of the unsaturated ester was completely quenched by the PhSeCl. No cyclofunctionalization took place. Chloroselenide 24' had inter alia: ($CDCl_3$, 200 MHz)

δ 1.80 [-C$\underline{H}_2$CH(SePh)CH_2Cl]; 3.31 [-CH_2C$\underline{H}$(SePh)CH_2Cl]; 3.62, 3.88 [-CH_2CH(SePh)C$\underline{H}_2$Cl]. Chloroselenide 25' had inter alia: δ 1.98 [-C$\underline{H}_2$CH(Cl)CH_2SePh], 3.16, 3.38 [-CH_2CH(Cl)C$\underline{H}_2$SePh]; 4.10 [-CH_2C$\underline{H}$(Cl)CH_2SePh].

4-Pentenoic acid, trimethylsilyl ester.[123]

Triethylamine (285 mg, 2.82 mmol) was added to a stirred solution of 6 (256 mg, 2.56 mmol) in CH_2Cl_2 (7 mL). Chlorotrimethylsilane (306 mg, 2.82 mmol) was added dropwise and the mixture was stirred at room temperature overnight. The mixture was passed through a column of dry silica gel (2 x 15 cm) (130°C, 21 h) with CH_2Cl_2. The chromatography was carried out under nitrogen. Evaporation of the eluant (protection from moisture) followed by vacuum release to nitrogen resulted in an oil (300 mg, 68%) which had: IR (CCl_4) 1718 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.31 (s),[124] 2.20—2.62 (m, 4H), 4.90—5.24 (m, 2H), 5.54—6.08 (m, 1H).

2-(Phenylseleno)hexan-1-ol.

Hexanal (500 mg, 4.99 mmol) was added to a stirred solution of PhSeCl (1.15 g, 6.00 mmol) in EtOAc (30 mL) according to the literature procedure.[72a] Concentrated HCl (3 drops) was added and the mixture was stirred for 18 h at room temperature. Evaporation of the solvent

and column chromatography over silica gel (3 x 60 cm) with 14:1 heptane—EtOAc gave 2-(phenylseleno)hexanal (243 mg, 0.952 mmol) as a homogeneous oil (TLC, silica gel, 14:1 heptane—EtOAc). The oil was dissolved in 95% EtOH (7 mL) and $NaBH_4$ (36 mg, 0.952 mmol) was added. After a stirring period of 15 min (TLC control) the excess of $NaBH_4$ was quenched with acetone (1 mL) and saturated aqueous $NaHCO_3$ (10 mL) was added.

The organic solvents were evaporated and the aqueous residue was extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was dried and evaporated. Column chromatography over silica gel (2 x 60 cm) with 7:1 heptane—EtOAc gave 2-(phenylseleno)hexan-1-ol (156 mg, 0.606 mmol) as a homogeneous (TLC, silica gel, 7:1 heptane—EtOAc) oil: IR (film) 3400, 3070 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.87 (t, J = 7Hz, 3H), 1.08—1.94 (m, 6H), 2.20—2.50 (broad, s, 1H), 3.04—3.35 (m, 1H), 3.36—3.80 (m, 2H), 7.15—7.39 (m, 3H), 7.42—7.78 (m, 2H).

Treatment of 2-(phenylseleno)hexan-1-ol with HCl.

Dry HCl gas was passed through a solution of 2-(phenylseleno)hexan-1-ol (70.0 mg, 0.272 mmol) in CH_2Cl_2 for 5 min. The reaction vessel was slightly pressurized with HCl gas and the mixture was stirred for 5 min at room temperature. Evaporation of the solvent gave an oil

which had: IR (neat) 3070 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.72—1.04 (m, 3H), 1.05—2.26 (m, 6H), 3.00—3.62 (m, 2H), 3.78—4.20 (m, 1H), 7.14—7.40 (m, 3H), 7.42—7.80 (m, 2H).

Reaction of PhSeCl with CH_3CO_2H.

Benzeneselenenyl chloride (320 mg, 1.67 mmol) in CCl_4 (4 mL + 1 mL rinse) was added to CH_3CO_2H (100 mg, 1.67 mmol) in CCl_4 (4 mL) at room temperature. The mixture was stirred for 72 h during which time aliquots were removed periodically and examined by IR spectroscopy. Two bands were observed in the carbonyl region of the IR spectrum: 1710 cm^{-1} (s, intensity was constant) and 1764 cm^{-1} which appeared as a shoulder on the 1710 cm^{-1} band (w, intensity was constant). There was also a band at 3520 cm^{-1} which may indicate the presence of monomeric acid.

The orange color of the PhSeCl remained in the reaction mixture throughout the 72 h period.

Reaction of PhSeCl with NaOAc.

Benzeneselenenyl chloride (298 mg, 1.56 mmol) in CCl_4 (4 mL + 1 mL rinse) was added to anhydrous $NaOAc^{125}$ (100 mg, 1.22 mmol) in CCl_4 (4 mL) at room temperature. Aliquots of the mixture were removed periodically and examined by IR spectroscopy. Four bands were observed

in the carbonyl region of the IR spectrum: 1710 cm^{-1} (m, intensity increased), 1765 cm^{-1} (m, intensity increased), 1810 cm^{-1} (w, intensity increased) appeared as a shoulder on band at 1834 cm^{-1} (m, intensity increased). The color of the reaction mixture became bright yellow over ca. 2 h.

Attempted Preparation of Phenylselenoacetate.

Benzeneselenenyl chloride (200 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was added to AgOAc (174 mg, 1.04 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 15 min at room temperature. During the stirring period the color due to PhSeCl was discharged and a fine white precipitate formed. The resulting bright yellow liquid was transferred via syringe to a dry centrifuge tube (sealed with a septum) and any suspended solid was separated from the liquid by centrifugation. A small aliquot of this liquid was used to obtain a solution IR spectrum: IR (CH_2Cl_2) 1710 cm^{-1} (s), 1765 cm^{-1} (m), 1780 cm^{-1} (w), 1824 cm^{-1} (m).

The liquid was transferred to a flask and the solvent was evaporated resulting in a yellow solid. Oil pump evacuation and characterization of the residue by IR, ^{1}H-NMR and ^{13}C-NMR identified the solid as $(PhSe-)_2$ containing a few trace impurities.

Repetition of this experiment using CCl_4 as the solvent instead of CH_2Cl_2 gave similar results.

Methyl 2,4-Dinitrobenzeneselenenate.

2,4-Dinitrobenzeneselenenyl bromide[126] (150 mg, 0.460 mmol) in methanol (2 mL + 1 mL rinse) was added to AgOAc (90 mg, 0.539 mmol) in methanol (2 mL) according to the literature procedure.[33f] The mixture was refluxed overnight (protection from light) and filtered hot. Cooling of the filtrate resulted in precipitation of orange crystals (70 mg) which had: mp 135°—136°C, IR ($CDCl_3$) 1580, 1520, 1340 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 4.00 (s, 3H), 8.16 (d, J = 10 Hz, 1H), 8.58 (dd, J = 10, 2 Hz, 1H), 9.20 (d, J = 2 Hz, 1H); exact mass, m/e 277.9445 [calcd. for $C_7H_6N_2O_5{}^{80}Se$, m/e 277.9442].

Treatment of 41 with HCl.

A saturated solution of HCl in Et_2O[127] (3 drops) was added to 41 (12.0 mg, 0.047 mmol) in Et_2O (1 mL) at room temperature. The solution was stirred for 1 h before the solvent was evaporated and IR and NMR spectra of the residue were taken. An examination of the spectra revealed that conversion to 6a had occurred.

Treatment of 34a with HCl.

A saturated solution of HCl in Et_2O[127] (2 drops) was added to 34a (37.9 mg, 0.010 mmol) in Et_2O (1 mL) at room temperature. The solution was stirred overnight, the solvent was evaporated, and IR and NMR spectra of the residue were obtained. Inspection of the spectral data revealed that conversion to 34b had occurred.

Phenylselenoacetaldehyde.

The literature procedure[62] was followed except that benzeneselenenyl chloride and a large (ten-fold) excess of ethyl vinyl ether were used.

(Formylmethyl)phosphonic acid diethyl ester.[128]

Triethylphosphite (25.0 g, 150 mmol) was added to a 250 mL round-bottomed flask containing chloroacetaldehyde diethyl acetal (26.4 g, 173 mmol). The flask, equipped with a reflux condenser[129] and a magnetic stirring bar, was placed in an oil bath and heated (180°C) for 48 h while being stirred. The mixture was cooled and fractionally distilled (twice) to give the diethyl acetal of (formylmethyl)phosphonic acid diethyl ester (11.0 g, 29%), bp (74°C, 0.015 mm), NMR ($CDCl_3$, 100 MHz) δ 1.08-1.50 (m, 12H), 2.16 (dd, J = 18, 6 Hz, 2H), 3.32-3.82 (m, 4H), 3.90-4.30 (m, 4H), 4.88 (q, J = 6 Hz, 1H).

Dowex 50 W x 12 resin[130] (15 mL) was added to a solution of the acetal (7.00 g, 27.5 mmol) in H_2O (50 mL). The mixture was stirred for 19 h (VPC control[131]), filtered and the filtrate was continuously extracted with Et_2O (100 mL) for 18 h. The ethereal solvent was then evaporated, resulting in a wet residue which was dissolved in benzene (100 mL). The benzene was evaporated and the

resulting residue was fractionally distilled to give 58 (1.02 g, 20%) bp (64°C, 0.025 mm) IR (film) 1725 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.36 (t, J = 6 Hz, 6H), 3.09 (dd, J = 23, 3 Hz, 2H), 4.04-4.30 (m, 4H), 9.68 (td, J = 3, 1 Hz, 1H).

Methylselenoacetaldehyde.

Dimethyldiselenide[132] (2.00 g, 10.6 mmol) was placed in a three neck round bottomed flask which was equipped with a thermometer, a solid addition tube containing $NaBH_4$ (870 mg, 23.0 mmol) and sealed with a septum. Inlet and exit needles for nitrogen were inserted and EtOH (55 mL) was added. The flask was immersed in an ice bath and $NaBH_4$ was added slowly while stirring the mixture. Once gas evolution ceased and the solution was colorless the contents of the flask was cooled to 10°C and chloroacetaldehyde dimethyl acetal (3.51 g, 23.0 mmol) in EtOH (8 mL + 2 mL rinse) was added. The solution was warmed to room temperature and refluxed for 18 h (a dry condenser was placed on the flask). The solution was then filtered, diluted with H_2O (200 mL) and extracted with pentane (4 x 100 mL). The combined pentane fractions were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL) and were then dried. The solvent was evaporated and the residue flask chromatographed over silica gel

(5 x 13 cm) with 20:1 heptane—EtOAc to give the acetal (1.50 g, 33%) as an oil. Hydrolysis to the aldehyde was effected by vigorously stirring the acetal (1.50 g, 7.10 mmol) in Et_2O (50 mL) and aqueous HCl (0.1 N, 50 mL) overnight. The Et_2O layer was isolated and the aqueous layer was extracted with more Et_2O (2 x 25 mL). The combined ethereal fractions were washed with saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL) and were dried. Evaporation of the solvent and distillation of the residue gave the aldehyde (473 mg, 16% overall) as an oil (bp 83°C,[133] 25 mm): IR (film) 1705 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.88 (s, 3H), 3.11 (d, J = 4Hz, 2H), 9.31 (t, J = 4Hz, 1H); exact mass, m/e 137.9584 (calcd. for $C_3H_6O^{80}Se$, m/e 137.9584).

[(3-Ethenyl-2-methyl-1-cyclopenten-1-yl)oxy]trimethylsilane 61a.

The literature procedure[134] was followed except commercial vinylmagnesium bromide (adjusted to 0.68 M) in THF was used instead of vinylmagnesium chloride. It is important to cool the reaction mixture (to about -70°C) immediately after addition of Cu(I)I.

[(3-Ethenyl-1-cyclohexen-1-yl)oxy]trimethylsilane 62a.

The initial stages employed for 61a were followed using vinylmagnesium bromide (34.8 mL, 0.68 M in THF, 23.6 mmol) Cu(I)I (2.43 g, 12.8 mmol), cyclohex-2-enone (1.00 g, 10.4 mmol), Me_3SiCl (3.20 mL, 25.2 mmol), HMPA (6.60 mL) and Et_3N (4.73 mL, 33.9 mmol). After the 2 h warm-up period the solution was poured into a vigorously stirred mixture of pentane (50 mL), Et_2O (50 mL) and water (50 mL). The resulting mixture was filtered. The organic phase was washed with saturated aqueous $NaHCO_3$ (25 mL) and with brine (25 mL). It was then dried and evaporated. The residue was distilled (bp 72°C, 3 mm) and subjected to flash chromatography over silica gel (2 x 15 cm) with 433:1 hexane—$CHCl_3$. Appropriate fractions were combined and Kugelrohr distillation (bp 72°C, 3 mm) gave 62a (777 mg, 38%) as a homogeneous (TLC, silica gel, 433:1 hexane—$CHCl_3$) colourless liquid: IR ($CDCl_3$) 1662 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.22 (s),[124] 1.1—2.1 (m, 6 H), 2.7—2.98 (br, s, 1 H), 4.7—5.1 (m, 3 H), 5.58—5.96 (m, 2 H); exact mass m/e 196.1276 (calcd for $C_{11}H_{20}OSi$, m/e 196.1283). Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28; H, 10.27. Found: C, 67.46; H, 10.25. Satisfactory O or Si analyses could not be obtained. The experiment was repeated by a procedure involving the use of a catalytic amount of Cu(I)I[135] but the yield was

not improved significantly.

[3-(1-Methylethenyl)-1-cyclohexen-1-yl)oxy]trimethylsilane 63a.[136]

A few drops of 2-bromopropene were added to magnesium (537 mg, 22.1 mmol), THF (15 mL), and a crystal of iodine. When the Grignard reaction had started, more 2-bromopropene (total used = 3.66 g, 30.3 mmol) in THF (5 mL + 1 mL rinse) was added over 13 min and the reaction mixture was then refluxed for 15 min. It was diluted with THF (15 mL) and cooled to 0°C. Anhydrous Cu(I)I (210 mg, 1.10 mmol) was added and a solution of cyclohex-2-enone (1.00 g, 10.4 mmol) in THF (14 mL + 1 mL rinse) was injected over a 10 min period while stirring. The resulting mixture was stirred at 0°C for an additional 1 h and the experiment was completed as for the preparation of 61a but at 0°C (instead of -60°C), using Me_3SiCl (3.20 mL, 25.2 mmol), HMPA (6.60 mL), and Et_3N (4.73 mL, 33.9 mmol). After being allowed to warm to room temperature for 2 h, the mixture was shaken in a separatory funnel containing pentane (100 mL) and aqueous NH_4Cl (10% w/w, 50 mL). The aqueous layer was extracted with Et_2O (2 x 25 mL) and the combined pentane—Et_2O extracts were dried, evaporated, and distilled to afford 63a (1.89 g, 86%) as a colorless,

homogeneous (TLC, silica gel, 433:1 hexane—$CHCl_3$) liquid, better than 98% pure by VPC analysis: bp 84°C (2.9 mm); IR (film) 1662 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.2 (s),[124] 1.24—2.2 (m, 9 H), 2.7—2.95 (br, 1 H), 4.66—4.82 (m, 3 H); exact mass m/e 210.1438 (calcd for $C_{12}H_{22}OSi$, m/e 210.1439). Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.54. Found: C, 68.59; H, 10.60. Satisfactory O and Si analyses could not be obtained.

2-(1-Hydroxy-2-methylselenoethyl)-4-tert-butylcycloxanone.

The procedure for 66b was followed using butyllithium (1.20 mL, 1.52 M, hexane solution, 1.82 mmol), diisopropylamine (277 mg, 2.73 mmol) in Et_2O (6 mL), 4-tert-butylcyclohexanone (282 mg, 1.82 mmol) in Et_2O (4 mL + 1 mL rinse), chlorodibutylborane (294 mg, 1.82 mmol) in Et_2O (6 mL + 1 mL rinse), methylselenoacetaldehyde (250 mg, 1.82 mmol) in Et_2O (7 mL + 1 mL rinse) and trimethylamine N-oxide (411 mg, 5.47 mmol) in MeOH (7 mL + 2 mL rinse). The solvent was evaporated and the residue was flash chromatographed (twice) over silica gel (2 x 15 cm) with 5:1 heptane—EtOAc to give the hydroxyketone (187 mg, 33%) as a homogeneous (TLC, silica gel, 5:1 heptane—EtOAc) oil: IR (film) 1710 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.88 and 0.90 (s, 9 H), 1.16—1.70 (m, 4 H), 1.91—2.22 (m,

incorporating two singlets at δ 2.00 and δ 2.02, 5 H), 2.24—2.88 (m, 5 H), 4.09—4.23 (m, 1 H).

2-(1-Hydroxy-2-diethylphosphonoethyl)cyclohexanone.

The procedure for 72b was followed using N,N-diisopropylethylamine (266 mg, 2.06 mmol) in Et_2O (1 mL + 1 mL rinse), dibutylboron triflate (512 mg, 1.98 mmol) in Et_2O (3 mL), cyclohexanone (183 mg, 1.86 mmol) in Et_2O (2 mL + 1 mL rinse), 58 (349 mg, 1.94 mmol) in Et_2O (2 mL + 1 mL rinse) and trimethylamine N-oxide (422 mg, 5.62 mmol) in MeOH (2 mL + 1 mL rinse). The mixture was evaporated and chromatographed over silica gel (2 x 60 cm) with EtOAc to give the hydroxyketone (196 mg, 35%) as a homogeneous (TLC, silica gel, EtOAc) oil which solidified on standing: mp, 165°C (decomposed); IR (film) 1708 cm^{-1}; NMR (CD_3OD, 200 MHz) δ 1.23-1.38 (m, 6 H), 1.48—2.70 (m, 11 H), 4.00—4.22 (m, 4H), 4.24—4.43 (m, 1H); exact mass, m/e 278.1292 (calcd for $C_{12}H_{23}O_5P$, m/e 278.1283).

2-(1-Hydroxy-2-phenylselenoethyl)-2-methylcyclohexanone 60b.

a) Via the silyl enol ether: Methyllithium (1.47 M, Et_2O solution, 1.71 mL, 2.51 mmol) was injected at room temperature into a stirred solution of the silyl enol ether 60a[64a] (463 mg, 2.51 mmol) in Et_2O (6 mL). After a further period of 1.5 h the mixture was cooled to 0°C and

$ZnCl_2$ (1.82 mL of a saturated Et_2O solution, 63a 1.26 mmol) was added dropwise. The mixture was left for 10 min at 0°C and phenylselenoacetaldehyde (500 mg, 2.51 mmol) in Et_2O (2.5 mL + 0.5 mL rinse) was injected rapidly (main portion added over ca. 3 sec). The mixture was stirred for a further 5 min and was then shaken with aqueous NH_4Cl (10% w/w, 10 mL). The Et_2O layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and with brine (10 mL). It was then dried and evaporated. Flash chromatography over silica gel (5 x 15 cm) with 4:1 heptane—EtOAc gave 60b (745 mg, 95%) as a pale yellow oily mixture of diastereoisomers [ca. 59:41 (NMR)] which were partially resolvable by TLC (4:1 heptane—EtOAc): IR ($CDCl_3$) 1693 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.11 (s, 1.24H), 1.20 (s, 1.81H), 1.50—3.18 (m, 11H), 3.96—4.10 (m, 1H), 7.18—7.38 (m, 3H), 7.48—7.64 (m, 2H); exact mass m/e 312.0627 (calcd for $C_{15}H_{20}O_2{}^{80}Se$, m/e 312.0629). Anal. Calcd for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.48; O, 10.28. Found: C, 57.97; H, 6.44; O, 10.40.

The oil partially crystallized upon storage at ca. -20°C. Dissolution of the material in the minimum volume of boiling 10:1 heptane—EtOAc gave a solution which deposited the crystalline isomer [containing less than 3 mole % of the liquid isomer (NMR)]: mp 78—80°C; IR ($CDCl_3$) 1708—1690 cm^{-1}; NMR ($CDCl_3$, 200 MHz) 1.20 (s,

3H), 1.54—2.04 (m, 6H), 2.24—2.60 (m, 3H), 2.84—3.16 (m, 2H), 4.01 (dd, J = 10.5, 2.7 Hz, 1H), 7.22—7.36 (m, 3H), 7.50—7.62 (m, 2H); exact mass m/e 312.0627 (calcd for $C_{15}H_{20}O_2{}^{80}Se$, m/e 312.0629). Anal. Calcd for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.48; O, 10.28. Found: C, 57.57; H, 6.53; O, 9.99.

The proportion of the crystalline isomer varied from run to run and sometimes it was nearly the exclusive product.

b) Via the enol borinate: Lithium diisopropylamide was prepared following the procedure for 65b using butyllithium (357 mL, 1.52 M hexane solution, 5.42 mmol) and diisopropylamine (548 mg, 5.42 mmol) in Et_2O (18 mL). The solution was cooled to -78°C and 2-methylcyclohexanone (1.22 g, 10.8 mmol) in Et_2O (12 mL + 2 mL rinse) was added rapidly. The solution was warmed to room temperature and stirred for 1 h. After cooling to -20°C the condensation with phenylselenoacetaldehyde was accomplished following the procedure for 66b, using chlorodibutylborane (870 mg, 5.42 mmol) in Et_2O (17 mL + 4 mL rinse), phenylselenoacetaldehyde (1.08 g, 5.42 mmol) in Et_2O (20 mL + 4 mL rinse) and trimethylamine N-oxide (1.22 g, 16.3 mmol) in MeOH (20 mL + 7 mL rinse). Flash chromatography (twice) over silica gel (5 x 15 cm) with 4:1 heptane—EtOAc gave a 5.2:1 mixture (NMR) of 60b and 73b (787 mg, 46%) as a mixture of diastereoisomers (three spots TLC, 4:1

heptane—EtOAc).

3-Ethenyl-2-(1-hydroxy-2-phenylselenoethyl)-2-methylcyclopentanone 61b.

The reaction was carried out exactly as for the preparation of 60b using methyllithium (1.80 M, Et_2O solution, 0.72 mL, 1.30 mmol), silyl enol ether 61a (255 mg, 1.30 mmol) in Et_2O (10 mL), $ZnCl_2$ (0.94 mL of a saturated Et_2O solution, 0.65 mmol) and phenylselenoacetaldehyde (259 mg, 1.30 mmol) in Et_2O (3 mL + 1 mL rinse). Flash chromatography over silica gel (5 x 20 cm) with 9:1 heptane—EtOAc gave 61b as two apparently homogeneous (TLC, silica gel, 9:1 heptane—EtOAc) selenides of combined weight 352 mg (83%). The material of higher R_f (255 mg, 60%) was an oil: IR ($CDCl_3$) 1732 cm^{-1} (broad); NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3H), 1.62—2.50 (m, 4H), 2.90—3.32 (m, 4H), 3.68 (dd, J = 10, 4 Hz, 1H), 5.04—5.15 (m, 2H), 5.71—5.92 (m, 1H), 7.22—7.32 (m, 3H), 7.44—7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 13.5, 24.9, 31.7, 38.0, 46.8, 54.6, 73.6, 116.9, 127.1, 129.1, 129.5, 132.7, 137.4, 222.3; exact mass m/e 324.0632 (calcd. for $C_{16}H_{20}O_2{}^{80}Se$, m/e 324.0638). Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.57; H, 6.25; O, 9.84.

The material of lower R_f (97.1 mg, 23%) solidified when stored at -20°C: mp 88—89°C (from 10:1 hexane—EtOAc);[137] IR ($CDCl_3$) 1738 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 1.48—2.48 (m, 4H), 2.60—2.80 (broad, s, 1H), 2.93 (dd, J = 12.0, 12.8 Hz, 1H), 3.12—3.28 (m, 2H), 3.84 (broad d, J = 12 Hz, 1H), 5.08—5.26 (m, 2H)), 5.76—5.98 (m, 1H), 7.16—7.32 (m, 3H), 7.40—7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 14.7, 25.6, 32.5, 38.0, 43.7, 55.1, 74.3, 116.9, 127.4, 129.3, 132.9, 138.8, 221.2; exact mass m/e 324.0628 (calcd for $C_{16}H_{20}O_2{}^{80}Se$, m/e 324.0630). Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.45; H, 6.23; O, 9.97.

3-Ethenyl-2-(1-hydroxy-2-phenylselenoethyl)cyclohexanone 62b.

The reaction was carried out exactly as for the preparation of 60b using methyllithium (1.75 M, Et_2O solution, 1.98 mL, 3.46 mmol), silyl enol ether 62a (680 mg, 3.46 mmol) in Et_2O (10 mL), $ZnCl_2$ (2.51 mL of a saturated Et_2O solution, 1.73 mmol) and phenylselenoacetaldehyde (689 mg, 3.46 mmol) in Et_2O (3 mL + 1 mL rinse). Flash chromatography over silica gel (5 x 15 cm) with 5:1 heptane—EtOAc gave 62b as two apparently[138] homogeneous (TLC, silica gel, 5:1 heptane—EtOAc) selenides of combined weight 1.01 g (90%). The material of higher R_f (619 mg, 55%) was an oil: IR ($CDCl_3$) 1692 cm^{-1};

NMR ($CDCl_3$, 200 MHz) δ 1.45—2.34 (m, 6H), 2.52—2.76 (m, 2H), 3.10—3.45 (m, 3H), 3.79 (broad dd, J = 16.8, 9.7 Hz, 1H), 4.93—5.18 (m, 2H), 5.47—5.69 (m, 1H), 7.15—7.39 (m, 3H), 7.41—7.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 26.2, 32.3, 32.7, 43.0, 47.3, 55.9, 70.3, 116.5, 127.1, 129.2, 129.6, 132.8, 139.9, 214.6; exact mass m/e 324.0628 (calcd for $C_{16}H_{20}O_2{}^{80}Se$, m/e 324.0628). Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.62; H, 6.20; O, 9.78.

The material of lower R_f (393 mg, 35%) crystallized on storage at -20°C; mp 46.5—47°C (from 10:1 heptane—EtOAc);[138] IR ($CDCl_3$) 1697 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.48—2.14 (m, 4H), 2.16—2.58 (m, 3H), 2.66 (broad dd, J = 10, 5.2 Hz, 1H), 2.88—3.46 (m, 3H), 3.88—4.16 (m, 1H), 4.90—5.06 (m, 2H), 5.54—5.78 (m, 1H), 7.18—7.40 (m, 3H), 7.42—7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 24.6, 31.8, 32.6, 41.9, 45.3, 58.5, 69.9, 115.8, 127.1, 129.0, 133.2, 140.2, 212.8; exact mass m/e 324.0627 (calcd for $C_{16}H_{20}O_2{}^{80}Se$, m/e 324.0628). Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.65; H, 6.16; O, 9.80.

Direct Condensation of Phenylselenoacetaldehyde to give 62b.

The initial stages employed for 61a were followed using vinylmagnesium bromide (17.4 mL, 0.68 M in THF,

11.8 mmol), Cu(I)I (1.22 g, 6.43 mmol) and cyclohex-2-enone (500 mg, 5.20 mmol). After addition of the ketone the mixture was stirred for 45 min at -30°C. It was then warmed to 0°C (10 min) and phenylselenoacetaldehyde (1.04 g, 5.22 mmol) in THF (4 mL + 1 mL rinse) was injected rapidly. The solution was stirred for 5 min and worked up as for 62b. Flash chromatography of the product over silica gel (5 x 15 cm) with 4:1 heptane—EtOAc gave 62b (1.20 g, 71%) as a mixture of diastereoisomers which still contained impurities (TLC, silica gel, 4:1 heptane—EtOAc). Further attempts to purify the product by chromatography were unsuccessful.

2-(1-Hydroxy-2-phenylselenoethyl)-3-(1 methylethenyl)-cyclohexanone 63b.

The reaction was carried out exactly as for the preparation of 60b using methyllithium (1.75 M, Et_2O solution, 2.72 mL, 4.75 mmol), silyl enol ether 63a (1.00 g, 4.75 mmol) in Et_2O (11 mL), $ZnCl_2$ (3.45 mL of a saturated Et_2O solution, 2.38 mmol) and phenylselenoacetaldehyde (946 mg, 4.75 mmol) in Et_2O (4 mL + 2 mL rinse). Flash chromatography over silica gel (5 x 20 cm) with 5:1 heptane—EtOAc gave 63b as two apparently homogeneous (TLC, silica gel, 5:1 heptane—EtOAc) selenides of combined weight 1.43 g (89%). The material of higher R_f (907 mg,

56%) crystallized on storage at -20°C: mp 30—31°C (from hexane); IR (film) 1693 cm^{-1}; NMR (d_6-DMSO, 200 MHz) δ 1.44—1.96 (m, including a singlet broadened by unresolved coupling at δ 1.64, 7H), 2.10—2.34 (m, 2H), 2.54—2.74 (m, 2H), 3.10—3.38 (m, 2H), 3.73 (broad q of d, J = 6.7, 2.5 Hz, 1H), 4.66—4.83 (m, 3H), 7.18—7.38 (m, 3H), 7.40—7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.2, 26.5, 31.1, 32.3, 43.1, 50.7, 53.9, 70.5, 113.5, 126.9, 129.2, 129.9, 132.3, 144.9, 215.6; exact mass m/e 338.0784 (calcd for $C_{17}H_{22}O_2{}^{80}Se$, m/e 338.0784). Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57; O, 9.49. Found: C, 60.49; H, 6.60; O, 9.48.

The material of lower R_f (523 mg, 33%) also crystallized on storage at -20°C; mp 40—41°C (from hexane); IR (film) 1697 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.52—1.90 (m, including a singlet broadened by unresolved coupling at δ 1.70, 6H), 1.92—2.12 (m, 1H), 2.17—2.53 (m, 3H), 2.83 (dd, J = 12, 4.8 Hz, 1H), 2.96—3.43 (m, 3H), 3.72—3.92 (m, 1H), 4.68—4.78 (m, 2H), 7.19—7.36 (m, 3H), 7.46—7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.3, 24.9, 30.9, 32.2, 42.2, 49.0, 56.6, 70.0, 113.2, 127.0, 129.0, 130.0, 133.2, 145.0, 213.4; exact mass, m/e 338.0784 (calcd for $C_{17}H_{22}O_2{}^{80}Se$, m/e 338.0784). Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57; O, 9.49. Found: C, 60.27; H, 6.52; O, 9.45.

2,5-Dimethyl-2-(1-hydroxy-2-phenylselenoethyl)cyclohexanone 64b.

Butyllithium (1.52 M, hexane solution, 2.48 mL, 3.77 mmol) was injected dropwise at -78°C into a stirred solution of diisopropylamine (572 mg, 5.65 mmol) in Et_2O (15 mL) containing a few mg of 2,2'-dipyridyl. After stirring for 30 min 2,6-dimethylcyclohexanone (as a mixture of isomers, 480 mg, 3.78 mmol) in Et_2O (6 mL + 2 mL rinse) was added over a 15 min period. Stirring was continued for 30 min and the mixture was then allowed to warm to 0°C over about 30 min. Zinc chloride (2.73 mL of a saturated Et_2O solution, 1.88 mmol) was added dropwise. Stirring at 0°C was continued for 10 min and phenylselenoacetaldehyde (787 mg, 3.96 mmol) in Et_2O (4 mL + 2 mL rinse) was injected rapidly (main portion added over ca. 3 sec). The mixture was stirred 5 min and worked up as for 60b. Flash chromatography over silica gel (5 x 15 cm) with 4:1 heptane—EtOAc gave 64b (1.10 g, 89%) as a mixture of diastereoisomers that were partially resolvable by TLC (silica gel, 4:1 heptane—EtOAc): IR (film) 1703 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.85—1.09 (m, 6H), 1.15—2.1 (m, 6H), 2.48—3.3 (m, 4H), 4—4.2 (m, 1H), 7.2—7.38 (m, 3H), 7.45—7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 15.1, 17.1, 20.7, 32.5, 36.0, 37.7, 41.6, 52.7, 72.6, 127.7, 129.4, 133.4, 214.5.

Signals due to a minor isomer were present at δ 15.0, 16.7, 20.3, 33.2, 35.9, 36.7, 42.8, 70.9, 133.7; exact mass, m/e 326.0786 (calcd for $C_{16}H_{22}O_2{}^{80}Se$, m/e 326.0785). Anal. Calcd for $C_{16}H_{22}O_2Se$: C, 59.08; H, 6.82; O, 9.84. Found: C, 59.02; H, 6.78; O, 9.56.

2-(1-Hydroxy-2-phenylselenoethyl)-2,5,5-trimethylcyclohexanone 65b.

Butyllithium (1.54 M, hexane solution, 2.45 mL, 3.77 mmol) was injected dropwise at -78°C into a stirred solution of diisopropylamine (572 mg, 5.65 mmol) in Et_2O (15 mL) containing a few mg of 2,2'-dipyridyl. The solution was kept for 30 min, then warmed to -30°C and stirred for 30 min. 2,2,6-Trimethylcyclohexanone (528 mg, 3.77 mmol) in Et_2O (6 mL + 2 mL rinse) was added over 15 min. The reaction mixture was kept at -30°C for 1.25 h and was then warmed to 0°C over 30 min. Zinc chloride (2.73 mL of a saturated Et_2O solution, 1.88 mmol) was added dropwise and stirring at 0°C was continued for 5 min. Phenylselenoacetaldehyde (750 mg, 3.77 mmol) in Et_2O (4 mL + 2 mL rinse) was injected rapidly (main portion added over ca. 3 sec). The mixture was stirred 5 min and worked up as for 60b. Flash chromatography over silica gel (5 x 15 cm) with 4:1 heptane—EtOAc gave 65b (966 mg, 75%) as a mixture [73:27 (NMR)] of diastereoisomers that

were not resolved by TLC (silica gel, 4:1 heptane—EtOAc): IR (film) 1689 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.03 (s, 0.8H), 1.07 (s, 2.2H), 1.11 (s, 0.8H), 1.13 (s, 0.8H), 1.15 (s, 2.2H), 1.22 (s, 2.2H), 1.42—2.14 (m, 6H), 2.72—2.95 (m, 0.5H), 2.96—3.14 (m, 1.5H), 3.56—3.78 (broad s, 1H), 3.83—4.06 (m, 1H), 7.17—7.34 (m, 3H), 7.43—7.60 (m, 2H); exact mass, m/e 340.0933 (calcd for $C_{17}H_{24}O_2{}^{80}Se$, m/e 340.0942). Anal. Calcd for $C_{17}H_{24}O_2Se$: C, 60.17; H, 7.13; O, 9.43. Found: C, 60.19; H, 7.18; O, 9.34.

2-(1-Hydroxy-2-phenylselenoethyl)cyclohexanone 66b.

LDA was prepared as in the synthesis of 65b using butyllithium (1.52 M, hexane solution, 3.74 mL, 5.68 mmol) and diisopropylamine (864 mg, 8.54 mmol) in Et_2O (18 mL) containing a few mg of 2,2'-dipyridyl. The solution was warmed to -20°C over 30 min and cyclohexanone (560 mg, 5.70 mmol) in Et_2O (10 mL + 4 mL rinse) was injected over 15 min. Chlorodibutyl borane[139] (915 mg, 5.70 mmol) in Et_2O (14 mL + 7 mL rinse) was added over 3 min and the solution was stirred for 1 h. Phenylselenoacetaldehyde (1.13 g, 5.69 mmol) in Et_2O (18 mL + 6 mL rinse) was added at -30°C at a fast dropwise rate and stirring at -30°C was continued for 2 h. The mixture was then cooled to -78°C and trimethylamine N-oxide[69] (1.28 g, 17.1 mmol) in MeOH (27 mL) was injected dropwise. The cold

bath was removed and stirring was continued overnight. The mixture was evaporated and flash chromatography (twice) over silica gel (5 x 15 cm) with 5:1 heptane—EtOAc gave 66b (1.33 g, 78%) as an apparently homogeneous[140] (TLC, silica gel, 5:1 heptane—EtOAc) oil: IR (film) 1704 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.38—2.47 (m, 9H), 2.49—2.79 (m, 1H), 2.97—3.35 (m, 2H), 3.85—4.01 (m, 0.6H), 4.13—4.28 (m, 0.4H), 7.21—7.39 (m, 3H), 7.47—7.67 (m, 2H); exact mass, m/e 298.0481 (calcd for $C_{14}H_{18}O_2{}^{80}Se$, m/e 298.0472). Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10; O, 10.76. Found: C, 56.80; H, 6.26; O, 10.61.

3-Ethenyl-2-(1-hydroxy-2-phenylselenoethyl)cyclooctanone 67b.[141]

Anhydrous Cu(I)I (3.85 g, 16.2 mmol) was added from a side-arm addition tube to a magnetically stirred solution of vinylmagnesium bromide (1.28 M, THF solution, 25.3 mL, 32.4 mmol) at -5°C. The ice-bath was immediately replaced by an acetone dry-ice bath at -45°C. Cyclooctenone[142] (2.01 g, 16.2 mmol) in Et_2O (2.5 mL + 0.5 mL rinse) was injected dropwise over 2 min and the mixture was kept 2 h at -45°C. It was then brought to ice-bath temperature (over about 10 min) and phenylselenoacetaldehyde (3.21 g, 16.2 mmol) in Et_2O (12 mL + 1 mL rinse) was injected rapidly (main fraction added over ca. 10 sec).

Stirring was continued for 5 min and the mixture was partitioned between saturated aqueous NH_4Cl (150 mL) and Et_2O (1 x 150, 2 x 25 mL). The combined organic extract was washed with brine, dried, and evaporated. Flash chromatography over silica gel (5 x 25 cm) with 4:1 hexane—EtOAc gave an oily liquid (1.84 g) and crystallization from hexane afforded 67b (1.42 g, 25%): mp 58—59°C. The mother liquors and the mixed fractions from the flash chromatography were evaporated and flash chromatography (5 x 20 cm) using the above system followed by crystallization provided a further crop (523 mg, 9%) of 67b: mp 58.5—59°C. The compound had: IR (CCl_4) 1705 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.18—1.90 (m, 7H), 1.94—2.59 (m, 4H), 2.60—3.00 (broad s, 1H), 3.16—3.40 (m, 3H), 3.70—3.86 (m, 1H), 4.80—5.06 (m, 2H), 5.48—5.74 (m, 1H), 7.16—7.34 (m, 3H), 7.40—7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 22.8, 23.2, 28.5, 32.5, 33.4, 46.1, 46.6, 54.5, 71.3, 115.3, 127.3, 129.0, 133.3, 140.9, 218.3; exact mass, m/e 352.0936 (calcd for $C_{18}H_{24}O_2{}^{80}Se$, m/e 352.0941). Anal. Calcd for $C_{18}H_{24}O_2Se$: C, 61.53; H, 6.89; O, 9.11. Found: C, 61.35; H, 6.85; O, 8.96.

2-(1-Hydroxy-2-phenylselenoethyl)cyclodecanone 68b.

Apart from the fact that the cyclodecanone was added over 1.5 h (as opposed to 15 min) the procedure for 65b

was followed using butyllithium (1.40 M, hexane solution, 3.47 mL, 4.86 mmol), diisopropylamine (492 mg, 4.86 mmol) in Et_2O (13 mL), cyclodecanone (750.0 mg, 4.86 mmol) in Et_2O (6 mL + 3 mL rinse), $ZnCl_2$ (3.52 mL of a saturated Et_2O solution, 2.43 mmol), and phenylselenoacetaldehyde (968 mg, 4.86 mmol) in Et_2O (4 mL + 1 mL rinse). Flash chromatography over silica gel (5 x 15 cm) with 4:1 heptane—EtOAc gave 68b (1.68 g, 85%) as a homogeneous (TLC, silica gel, 4:1 heptane—EtOAc) oil which solidified on standing and was recrystallized from hexane: mp 44.5—45.5°C; IR (film) 1697 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.06—1.96 (m, 14H), 2.24—2.50 (m, 1H), 2.63—2.83 (m, 1H), 2.84—3.24 (m, 4H), 3.63—3.84 (m, 1H), 7.23—7.42 (m, 3H), 7.45—7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 23.3, 24.3, 24.4, 25.3, 25.4, 25.5, 26.3, 33.3, 43.9, 56.2, 71.5, 127.4, 129.3, 133.0, 133.2, 216.9; exact mass, m/e 354.1098 (calcd for $C_{18}H_{26}O_2{}^{80}Se$, m/e 354.1098). Anal. Calcd for $C_{18}H_{26}O_2Se$: C, 61.18; H, 7.42; O, 9.06. Found: C, 61.28; H, 7.50; O, 9.23.

2-(1-Hydroxy-1-methyl-2-phenylselenoethyl)cyclohexanone 69b.

LDA was prepared as described for 65b from butyllithium (0.99 M, hexane solution, 5.15 mL, 5.10 mmol) diisopropylamine (772 mg, 7.63 mmol) in Et_2O (15 mL) containing a few mg of 2,2'-dipyridyl. The solution was kept at -78°C

for 30 min and then warmed to -30°C over 30 min. Cyclohexanone (500 mg, 5.10 mmol) in Et_2O (8 mL + 2 mL rinse) was added over 10 min. The mixture was stirred for 20 min and then allowed to warm to 0°C over 15 min. Zinc chloride (3.69 mL of a saturated solution, 2.55 mmol) was added, stirring was continued for 5 min and phenylselenoacetone [72] (1.09 g, 5.10 mmol) in Et_2O (6 mL + 2 mL rinse) was injected rapidly (main portion added over ca. 6 sec). The mixture was stirred for 30 min at 0°C and then worked up as for 60b. Flash chromatography over silica gel (5 x 15 cm) with 10:1 heptane—EtOAc gave 65b (1.06 g, 67%) as a mixture (NMR) of two diastereoisomers that were partially resolvable by TLC (silica gel, 10:1 heptane—EtOAc): IR (film) 1692 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 1.7H), 1.36 (s, 1.3H), 1.39—2.4 (m, 8H), 2.55—2.72 (m, 0.44H), 2.77—2.94 (m, 0.50H), 3.0—3.55 (series of sharp singlets, 2.46H), 4.18 (s, 0.51H), 7.18—7.35 (m, 3H), 7.45—7.7 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.23 MHz) δ 24.5, 24.8, 25.1, 25.4, 27.9, 28.2, 29.5, 29.6, 39.9, 43.2, 43.4, 56.3, 58.5, 73.8, 126.9, 129.1, 129.5, 132.7, 132.9, 214.0, 216.1; exact mass, m/e 312.0631 (calcd for $C_{15}H_{20}O_2{}^{80}Se$, m/e 312.0629). Anal. Calcd for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.48; O, 10.28. Found: C, 57.88; H, 6.48; O, 10.31.

4-Hydroxy-5-(phenylseleno)pentan-2-one 72b.

N,N-Diisopropylethylamine (165 mg, 1.28 mmol) in Et_2O (1 mL + 0.5 mL rinse) was added to a stirred solution of dibutylboron triflate[65a] (318 mg, 1.23 mmol) in Et_2O at -78°C according to the literature procedure.[65a,b] Dry acetone[143] (67.4 mg, 1.16 mmol) in Et_2O (2 mL + 1 mL rinse) was added and the mixture was stirred for 30 min at -78°C. Phenylselenoacetaldehyde (231 mg, 1.16 mmol) in Et_2O (2 mL + 1 mL rinse) was then injected and the mixture was stirred for 2 h at -78°C. A solution of trimethylamine N-oxide[69] (262 mg, 3.49 mmol) in MeOH (2 mL + 1 mL rinse) was then added dropwise and after 30 min the cold bath was removed and the mixture was stirred overnight. The solution was evaporated and chromatographed over silica gel (2 x 60 cm) with EtOAc to give 72b (236 mg, 79%) as a homogeneous (TLC, silica gel, EtOAc) oil: IR (film) 1712 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 2.12 (s, 3H), 2.60—2.85 (m, 2H), 2.93—3.13 (m, 2H), 3.26 (broad s, 1H), 4.06—4.24 (m, 1H), 7.20—7.34 (m, 3H), 7.46—7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 15.08 MHz) δ, 30.7, 34.8, 49.0, 67.0, 127.4, 129.4, 132.9, 208.6; exact mass, m/e 258.0160 (calcd for $C_{11}H_{14}O_2{}^{80}Se$, m/e 258.0159). Anal. Calcd for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.49; O, 12.44. Found: C, 51.61; H, 5.51; O, 12.52.

2-(1-Hydroxy-2-phenylselenoethyl)-6-methylcyclohexanone 73b.

Butyllithium (1.32 mL, 1.35 M hexane solution, 1.78 mmol) was added dropwise to a stirred solution of diisopropylamine (271 mg, 2.68 mmol) in Et_2O (6 mL) at -78°C. The solution (which contained 2 mg of α,α'-bipyridyl) was stirred at -78°C (10 min) and then at -30°C (30 min). The mixture was cooled to -78°C and 2-methylcyclohexanone (200 mg, 1.78 mmol) in Et_2O (3.5 mL + 1 mL rinse) was added dropwise over a period of 30 min. The solution was stirred for an additional 10 min before chlorodibutylborane (286 mg, 1.78 mmol) in Et_2O (4.5 mL + 2 mL rinse) was added. The solution was then stirred for 15 min at -78°C and for 1 h at -30°C. After re-cooling the mixture to -78°C, phenylselenoacetaldehyde (355 mg, 1.78 mmol) in Et_2O (6 mL + 2 mL rinse) was injected and stirring was continued for 2 h before trimethylamine N-oxide (402 mg, 5.35 mmol) in MeOH (7 mL + 2 mL rinse) was added. The cold bath was removed and the mixture was allowed to warm to room temperature overnight. After solvent evaporation, the residue was dissolved in pentane (50 mL) and the resulting solution was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) and was then dried. Solvent evaporation and chromatography (twice) over silica gel (2 x 15 cm) with 4:1 heptane—EtOAc gave 73b (234 mg, 42%) as a

mixture of diastereoisomers (two spots by TLC, silica gel, 4:1 heptane—EtOAc): IR (film) 1700 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.95 (d, J = 6.4 Hz), 0.96 (d, J = 6.4 Hz), 1.08 (d, J = 7.0 Hz), 1.09 (d, J = 7.0 Hz) total integration, 3H; 1.04—2.46 (m, 7H), 2.48—2.79 (m, 1H), 2.89—3.40 (m, 3H), 3.82—4.26 (m, H), 7.15—7.42 (m, 3H), 7.46—7.68 (m, 2H); exact mass, m/e 312.0623 (calcd for $C_{15}H_{20}O_2{}^{80}Se$, m/e 312.0628).

Treatment of 66b with Et_3N and $SOCl_2$.[75]

Triethylamine (181 mg, 1.79 mmol) was added to a stirred solution of 66b (75.9 mg, 0.255 mmol) in CH_2Cl_2 (2 mL) at room temperature. Thionyl chloride (60.8 mg, 0.510 mmol) in CH_2Cl_2 (1 mL + 1 mL rinse) was added dropwise to the solution and stirring was continued overnight. The mixture was poured into CH_2Cl_2 (20 mL) and the resulting solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and was then dried. Evaporation of the solvent gave a residue containing the desired 2-ethenylcyclohexanone (NMR). Attempts to purify the product however, were unsuccessful.

Experiments similar to the one above, employing low temperature (-20°C) or bases such as pyridine or N,N-diisopropylethylamine instead of Et_3N were also unsuccessful. While the product could be detected (NMR),

purification was extremely difficult.

Treatment of 66b with butyllithium/NaI/HMPA/$SOCl_2$.

Butyllithium (0.50 mL, 1.35 M hexane solution, 0.673 mmol) was added dropwise to a stirred solution of 66b (200 mg, 0.673 mmol) in Et_2O (6 mL) at -30°C. Sodium iodide (215 mg, 1.35 mmol) and HMPA (128 mg, 0.714 mmol) in MeCN (4 mL + 1 mL rinse) was added and the mixture was stirred for 5 min. Thionyl chloride (161 mg, 1.35 mmol) in MeCN (9 mL + 1 mL rinse) was injected dropwise into the mixture and the resulting solution was stirred for an additional 30 min at -20°C. The mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with pentane (3 x 20 mL). The pentane extracts were washed with brine (50 mL) and dried, resulting in a clear yellow solution. Evaporation of the solvent yielded a residue which decomposed upon standing. No olefinic material could be detected (TLC) in the residue.

Treatment of 66b with NaH and o-phenylenephosphorochloridite.[75]

Sodium hydride (16.6 mg, 50% oil disp., 0.346 mmol) was added in one portion to 66b (103 mg, 0.346 mmol) in THF (7 mL). The mixture was stirred for 15 min and then o-phenylenephosphorochloridite (60.4 mg, 0.346 mmol) in

THF (3 mL + 1 mL rinse) was added dropwise. The mixture was stirred at room temperature for 18 h. None of the desired olefinic material was formed (TLC control).

Treatment of 60b with Me_3SiCl and NaI.

Sodium iodide (58.1 mg, 0.388 mmol) in MeCN (2 mL + 1 mL rinse) was added to 60b (121 mg, 0.388 mmol) in MeCN (2 mL). The mixture was stirred and Me_3SiCl (84.3 mg, 0.776 mmol) in MeCN (2 mL + 1 mL rinse) was added dropwise at room temperature. The mixture was stirred for 20 h and then refluxed for 17 h. The reaction was monitored (TLC) periodically for the formation of 60c. None was detected.

A similar experiment employing the addition of pyridine (one equivalent) prior to the addition of Me_3SiCl was also unsuccessful in producing 60c.

Treatment of 60b with Et_3N and Me_3SiCl.

Triethylamine (390 mg, 3.21 mmol) was added to a stirred solution of 60b (500 mg, 1.61 mmol) in THF (6 mL) at room temperature. Chlorotrimethylsilane (183 mg, 1.68 mmol) in THF (2 mL + 1 mL rinse) was added and the mixture was stirred for 48 h. The solvent was evaporated and the residue flash chromatographed over silica gel (3 x 15 cm) with 4:1 heptane—EtOAc to give 60b' (200 mg,

0.522 mmol) as a mixture of diastereoisomers (two spots by TLC, silica gel, 4:1 heptane—EtOAc): IR (film) 1710 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 6H), 0.18 (s, 3H), 1.04 (s, 1H), 1.14 (s, 2H), 1.52—2.68 (m, 8H), 2.80—3.24 (m, 2H), 4.28—4.42 (m, 1H), 7.16—7.38 (m, 3H), 7.42—7.64 (m, 2H).

Treatment of 66b with 1-(trimethylsilyl)-1H-imidazole.

1-(Trimethylsilyl)-1H-imidazole (194 mg, 1.38 mmol) was added to a stirred solution of 66b (206 mg, 0.693 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred overnight, evaporated and the residue flash chromatographed over silica gel (2 x 20 cm) with 10:1 heptane—EtOAc. Solvent evaporation gave 66b' (200 mg, 78%) as a mixture of diastereoisomers (two spots by TLC; silica gel, 10:1 heptane—EtOAc): IR (film) 1710 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.11 (s, 4.5H), 0.13 (s, 4.5H), 1.42—2.44 (m, 8H), 2.46—2.81 (m, 1H), 2.84—3.30 (m, 2H), 4.18—4.41 (m, 1H), 7.15—7.38 (m, 3H), 7.45—7.64 (m, 2H).

Treatment of 66b with Et_3N and CF_3SO_2Cl.

Triethylamine (306 mg, 3.02 mmol) was added to 66b (180 mg, 0.606 mmol) in CH_2Cl_2 (4.5 mL). Trifluoromethanesulfonyl chloride (306 mg, 1.82 mmol) in CH_2Cl_2 (4 mL +

1 mL rinse) was injected dropwise at room temperature over a 15 min period. The mixture was stirred for 1 h and then filtered through a column of silica gel (1 x 10 cm) with $CHCl_3$. Evaporation of the solvents left a residue which did not contain any olefinic material (NMR).

Treatment of 60b with NaH/trifluoroacetic anhydride/NaI.[77]

Sodium hydride (19.7 mg, 50% oil disp., 0.411 mmol) was added in one portion to a stirred solution of 60b (128 mg, 0.411 mmol) in THF:MeCN (1 mL:1 mL) at room temperature. After 15 min trifluoroacetic anhydride (86.3 mg, 0.411 mmol) was added dropwise to the mixture. After 5 min NaI (245 mg, 1.64 mmol) was added and the solution was stirred for 20 min. The solvent was then evaporated and the residue was dissolved in Et_2O (50 mL). After being washed with aqueous $NaHSO_3$ (5%, 50 mL), aqueous saturated $NaHCO_3$ (50 mL) and brine (50 mL), the solvent was dried and the Et_2O was evaporated. Inspection of the residue (NMR) revealed none of the desired product, 60c.

A similar experiment employing tert-butyllithium instead of NaH was also unsuccessful.

Treatment of 60b with phenylselenotrimethylsilane.

Phenylselenotrimethylsilane[144] (102 mg, 0.445 mmol) in THF (3 mL + 1 mL rinse) was added dropwise to a stirred

solution of 60b (116 mg, 0.303 mmol) in THF (4 mL) at room temperature. The mixture was stirred for 17 h and monitored (TLC) periodically. Since none of 60c was detected NaH (14.5 mg, 50% oil disp., 0.303 mmol) was added and the solution was stirred for 1 h and then refluxed for 2 h. No olefinic product was detected.

Treatment of 60b' with phenylselenotrimethylsilane.

Phenylselenotrimethylsilane (123 mg, 0.533 mmol) in THF (2 mL + 1 mL rinse) was added dropwise to a stirred solution of 60b' (146 mg, 0.381 mmol) in THF (4 mL) at room temperature. The mixture was stirred for 18 h at room temperature and refluxed for 2 h. The reaction mixture was monitored (TLC) periodically for the formation of 60c. None was detected.

Treatment of 60b with 1-ethyl-2-fluoropyridium tetrafluoroborate.[78]

A mixture of 60b (350 mg, 1.12 mmol) and Et_3N (137 mg, 1.34 mmol) in acetone[143] (3 mL + 1 mL rinse) was added to a stirred solution of 1-ethyl-2-fluoropyridinium tetrafluoroborate[78] (287 mg, 1.34 mmol) in acetone (1.6 mL) at 0°C. After 2 h LiI (181 mg, 1.38 mmol) was added in one portion and the mixture was refluxed for 2 h.

Since starting material was still present (TLC) the solution was refluxed for an additional 17 h. The solvent was then evaporated and the residue was dissolved in Et_2O (50 mL). The ethereal solution was washed with aqueous $NaHSO_3$ (5% w/w, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The solution was dried and the solvent was evaporated to give a residue which was chromatographed over silica gel (2 x 10 cm) with $CHCl_3$. Kugelrohr distillation (bp 85°C, 5 mm) afforded 60c (40.0 mg, 26%[145]) as a homogeneous (TLC, silica gel, $CHCl_3$) oil.

Treatment of 82 with 4-N,N-dimethylaminopyridine and carbonochloridothioic acid O-(3-chlorophenyl)ester.[146]

4-N,N-Dimethylaminopyridine (357 mg, 2.92 mmol) was placed in a 25 mL round bottomed flask containing 82[147] (214 mg, 0.631 mmol) and carbonochloridothioic acid O-(3-chlorophenyl)ester (131 mg, 0.631 mmol). The flask was purged with nitrogen and then immersed in a preheated oil bath (110°C). Once the mixture melted, the solution was stirred for 2 h, then cooled. The mixture was dissolved in Et_2O (50 mL) and the resulting solution was filtered and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). After drying the solution the solvent was evaporated and the residue was distilled in a Kugelrohr apparatus (bp 116°C, 15 mm) to give

trans-cyclododecene[120] (90.9 mg, 86%).

Treatment of 60b with NaH and carbonochloridothioic acid O-(3-chlorophenyl)ester.

Sodium hydride (22.2 mg, 50% oil disp., 0.463 mmol) was added to a stirred solution of 60b (144.2 mg, 0.463 mmol) in THF (3 mL) at room temperature. After stirring for 15 min carbonochloridothioic acid O-(3-chlorophenyl)-ester (95.9 mg, 0.463 mmol) in THF (2 mL + 1 mL rinse) was added and the mixture was monitored (TLC) periodically for the presence of 60c. A TLC taken 2 h after addition of the ester indicated complete decomposition of the reaction mixture.

An analogous experiment using 4-N,N-dimethylamino-pyridine instead of NaH was also unsuccessful in producing 60c.

Treatment of 60b with pyridine and carbonochloridothioic acid S-phenyl ester.

Pyridine (45.6 mg, 0.575 mmol) in CH_2Cl_2 (1.5 mL + 0.5 mL rinse) was added to a stirred solution of 60b (179 mg, 0.575 mmol) in CH_2Cl_2 (4 mL) at room temperature. Carbonochloridothioic acid S-phenyl ester[148] (99.4 mg, 0.576 mmol) in CH_2Cl_2 (2 mL + 1 mL rinse) was then added

dropwise over a 5 min period. The mixture was stirred for 24 h and was monitored (TLC) periodically for the formation of 60c. None was detected. Refluxing the mixture for 17 h was also unsuccessful in forming the desired product.

Similar experiments involving the use of 4-N,N-dimethylaminopyridine or NaH instead of pyridine were likewise ineffective.

2-Ethenyl-2-methylcyclohexanone 60c.[149]

(a) Triethylamine (2.17 mL, 15.6 mmol) was injected into a stirred solution of 60b [crystalline (low R_f) material] (941 mg, 3.02 mmol) in CH_2Cl_2 (25 mL). Methanesulfonyl chloride (1.09 g, 9.49 mmol) in CH_2Cl_2 (9 mL + 1 mL rinse) was injected over 1.5 h. The mixture was stirred for a further arbitrary period of 10 min and then poured into CH_2Cl_2 (50 mL). The mixture was washed with ice-cold HCl (0.1 N, 50 mL), with saturated aqueous $NaHCO_3$ (50 mL) and finally with brine (50 mL). It was dried and evaporated and the residue was distilled twice in a Kugelrohr apparatus (bp 83°C, 3 mm) to give 60c (344 mg, 82%) as a homogeneous (VPC) oil: IR (film) 1713 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 3H), 1.53—2.07 (m, 6H), 2.26—2.63 (m, 2H), 4.95—5.20 (m, 2H), 6.01 (dd, J = 18.4, 12 Hz, 1H). For analysis the ketone (from a different

experiment) was converted into its 2,4-dinitrophenylhydrazone (64% based on 60b): mp 157—158°C (from 95% EtOH). Exact mass, m/e 318.1325 (calcd for $C_{15}H_{18}N_4O_4$, m/e 318.1328). Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.48; H, 5.63; N, 17.77.

(b) Use of phosgene: Pyridine (0.11 mL, 1.36 mmol) was added to the hydroxyselenide 60b [crystalline (low R_f) material], 209 mg, 0.671 mmol) in Et_2O (10 mL). The solution was cooled to -78°C and $COCl_2$ (ca., 80 drops) was condensed into it. The flask was then closed with a septum and an exit needle, attached to a bubbler, was passed through the septum. The mixture was stirred for 18 h, during which period the cold bath attained room temperature. The solvent was removed under water pump vacuum (protection from moisture) and replaced by dry MeCN (10 mL). Anhydrous NaI (403 mg, 2.69 mmol) was added, the mixture was stirred for 18 h and the solvent was evaporated. The residue was stirred with Et_2O (50 mL) and the flask was rinsed with aqueous $NaHSO_3$ (10% w/w, 5 mL) and with Et_2O (10 mL). These extracts were mixed and the Et_2O layer was separated and washed with aqueous $NaHSO_3$ (10% w/w, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). It was dried and evaporated. The NMR spectrum (200 MHz) of the residue showed the presence of 60c (78%, using an internal standard).

In a similar experiment the reaction mixture was refluxed for 30 min after addition of the NaI. After work up the NMR spectrum (200 MHz) of the residue showed the presence of 60c (84%, using an internal standard).

2,3-Diethenyl-2-methylcyclopentanone 61c (From high R_f hydroxyselenide).

a) The procedure for 60c was followed using Et_3N (0.49 mL, 3.54 mmol); 61b (high R_f material, 220 mg, 0.679 mmol) in CH_2Cl_2 (8 mL); $MeSO_2Cl$ (246 mg, 2.15 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 1 h. The acid wash used in the isolation of 60c was omitted from the work-up. Kugelrohr distillation (twice) (bp 93°C, 3 mm) gave 61c (83.8 mg, 82%) as an oil containing ca. 3% of an impurity (VPC) judged by VPC—mass spectral analysis to be an isomer (presumably a geometric isomer): IR ($CDCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 3H), 1.73—1.97 (m, 1H), 2.05—2.57 (m, 3H), 2.71—2.88 (m, 1H), 5.07—5.26 (m, 4H), 5.70—5.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 16.2, 24.3, 36.5, 49.7, 115.3, 116.6, 136.6, 140.3; exact mass, m/e 150.1040 (calcd for $C_{10}H_{14}O$, m/e 150.1045). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.15; H, 9.40.

b) Use of phosgene: The procedure for 60c was followed using 61b (high R_f material, 193 mg, 0.597 mmol), pyridine (0.10 mL, 1.28 mmol) and $COCl_2$ (ca., 80 drops) in Et_2O (10 mL) and NaI (179 mg, 1.19 mmol) in MeCN (10 mL). The NMR spectrum (200 MHz) of the residue showed the presence of 61c (53%,[150] using an internal standard).

2,3-Diethenyl-2-methylcyclopentanone 61c (From low R_f hydroxyselenide).

The procedure for 60c was followed using Et_3N (0.21 mL, 1.47 mmol); 61b (low R_f material, 91.1 mg, 0.282 mmol) in CH_2Cl_2 (2.5 mL); $MeSO_2Cl$ (102 mg, 0.891 mmol) in CH_2Cl_2 (2.5 mL + 0.5 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. The mixture was poured into 2:1 pentane—Et_2O (75 mL), washed with ice-cold HCl (2% w/w, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and finally with brine (50 mL). The organic phase was dried and evaporated. Kugelrohr distillation (twice) (bp 92°C, 3 mm) gave 61c (35.7 mg, 84%) as a homogeneous (TLC, silica gel, 5:1 heptane—EtOAc or silica gel impregnated with 5% w/w $AgNO_3$, EtOAc) oil that was better than 99% pure by VPC: IR (film) 1742 cm^{-1}; exact mass, m/e 150.1043 (calcd for $C_{10}H_{14}O$, m/e 150.1044). The NMR spectrum (200 MHz) was identical to that of material obtained from the high R_f hydroxyselenide.

trans-2,3-Diethenylcyclohexanone 62c (From high R_f hydroxyselenide).

The procedure for 61c (low R_f) was followed using Et_3N (0.22 mL, 1.60 mmol); 62b (high R_f material, 100 mg, 0.308 mmol) in CH_2Cl_2 (5 mL); $MeSO_2Cl$ (112 mg, 0.974 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 1 h. The acid wash used in the isolation of 61c (low R_f) was omitted from the work-up. After evaporation of the organic extract, the residue was filtered through silica gel (2 x 3.5 cm) using 4:1 hexane—EtOAc. Kugelrohr distillation (50°C, 0.01 mm) then gave 62c (38 mg, 82%) as an apparently homogeneous (TLC, silica gel, 4:1 heptane—EtOAc) oil. VPC—mass spectral analysis of the mixture revealed two components: 62c and an isomer (probably the 2,3-cis isomer), in the ratio of 39:1.[151] 62c had: IR (film) 1712 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.54—2.25 (m, 4H), 2.25—2.58 (m, 3H), 2.87 (dd, J = 10.7, 8.5 Hz, 1H), 4.92—5.13 (m, 3H), 5.22—5.34 (m, 1H), 5.64—5.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 15.08 MHz) δ 25.6, 31.1, 41.5, 48.4, 60.4, 115.0, 118.6, 134.9, 140.7, 210.6; exact mass, m/e 150.1045 (calcd for $C_{10}H_{14}O$, m/e 150.1044). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.77; H, 9.49.

trans-2,3-Diethenylcyclohexanone 62c (From low R_f hydroxyselenide).

The procedure ~~for 61c~~ (low R_f) was followed using Et_3N (0.41 mL, 2.96 mmol); 62b (low R_f material, 184 mg, 0.569 mmol) in CH_2Cl_2 (5 mL), $MeSO_2Cl$ (206 mg, 1.80 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After evaporation of the organic extract, following work-up as described for 61c (low R_f), the residue was chromatographed over silica gel with 5:1 heptane—EtOAc but this process did not remove all impurities. The material, which contained no conjugated ketone (IR control), was distilled in a Kugelrohr apparatus (bp 60°C, 0.3 mm) to give the product (60.7 mg, 71%). VPC—mass spectral analysis revealed three isomeric components: 62c, probably its 2,3-cis-isomer, and 3-ethenyl-2-ethylidenecyclohexanone, in the ratio of 9.3:1:7.4.[151,152] The mixture had IR (film) 1712, 1689 cm^{-1}. The NMR spectrum ($CDCl_3$, 200 MHz) showed inter alia signals at δ 2.87 (dd, J = 10.7, 8.5 Hz) and δ 6.89 (dq, J = 7.5, 1.6 Hz) with areas in the ratio of 1.05:1.

trans-2-Ethenyl-3-(1-methylethenyl)cyclohexanone 63c.[53a] (From high R_f hydroxyselenide).

The procedure for 60c was followed using Et_3N (0.34 mL, 2.43 mmol); 63b (high R_f material, 162 mg, 0.480 mmol)

in CH_2Cl_2 (5 mL); $MeSO_2Cl$ (165 mg, 1.44 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After the work-up specified for 60c, the product was distilled twice in a Kugelrohr apparatus (bp 82°C, 0.1 mm) to yield 63c (70.7 mg, 89%) as a homogeneous (TLC, silica gel, 4:1 heptane—EtOAc) oil, better than 99% pure (VPC): IR (film) 1711 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.62—1.94 (m, including a singlet broadened by unresolved coupling at δ 1.70, 6H), 2.00—2.20 (m, 1H), 2.26—2.57 (m, 3H), 3.01 (dd, J = 11.4, 8.8 Hz, 1H), 4.69—4.82 (m, 2H), 4.90—5.24 (m, 2H), 5.59—5.82 (m, 1H); exact mass, m/e 164.1196 (calcd for $C_{11}H_{16}O$, m/e 164.1201. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.30; H, 9.83.

trans-2-(Ethenyl)-3-(1-methylethenyl)cyclohexanone 63c. (From low R_f hydroxyselenide).

The procedure for 61c (low R_f) was followed using Et_3N (0.47 mL, 3.35 mmol); 63b (low R_f material, 227 mg, 0.671 mmol) in CH_2Cl_2 (5 mL); $MeSO_2Cl$ (231 mg, 2.01 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After the work-up specified for 61c (low R_f), Kugelrohr distillation (twice) (bp 55°C, 0.01 mm), column chromatography over silica gel (1 x 15 cm) with 5:1 hexane—EtOAc and redistillation in

a Kugelrohr apparatus gave 63c (89 mg, 80%) as a colorless, homogeneous (TLC, silica gel, 5:1 heptane—EtOAc, or silica gel impregnated with 5% w/w $AgNO_3$, EtOAc) oil that was better than 98% pure by VPC and spectroscopically identical with material from high R_f hydroxyselenide.

2,6-Dimethyl-2-ethenylcyclohexanone 64c.

a) The procedure for 60c was followed using Et_3N (0.68 mL, 4.85 mmol); 64b (a mixture of diastereomers, 304 mg, 0.933 mmol) in CH_2Cl_2 (10 mL); $MeSO_2Cl$ (338 mg, 2.95 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After the work-up specified for 60c, Kugelrohr distillation (twice) (bp 90°C, 3.0 mm) afforded 64c (108 mg, 75%) that was better than 98% pure (VPC). The sample consisted of two isomers (VPC—mass spectral analysis) in the ratio of 34.5:1 (VPC) and had IR (film) 1710 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.00 (d, J = 7.1 Hz, 3H), 1.15 (s, 3H), 1.20—2.15 (m, 7H), 2.61—2.83 (m, 1H), 4.93—5.21 (m, 2H), 5.91—6.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 14.9, 22.0, 24.5, 37.0, 40.9, 42.1, 52.4, 115.2, 142.9, 214.3; exact mass, m/e 152.1195 (calcd for $C_{10}H_{16}O$, m/e 152.1201. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.90; H, 10.55.

b) Use of phosgene: The procedure for 60c was followed using 64b (323 mg, 0.994 mmol), pyridine (0.16 mL, 1.99 mmol) and $COCl_2$ (ca. 80 drops) in Et_2O (10 mL) and NaI (298 mg, 1.99 mmol) in MeCN (10 mL). The NMR spectrum (200 MHz) of the residue showed the presence of 64c (42%, using an internal standard).

2-Ethenyl-2,6,6-trimethylcyclohexanone 65c.

a) The procedure for 60c was followed using Et_3N (0.78 mL, 5.60 mmol); 65b (mixture of diastereomers, 364 mg, 1.07 mmol) in CH_2Cl_2 (10 mL); $MeSO_2Cl$ (389 mg, 3.39 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After the work-up specified for 60c, Kugelrohr distillation (twice) (bp 93°C, 3.2 mm) gave 65c (151 mg, 84%) as a homogeneous (TLC, silica gel, 4:1 heptane—EtOAc) oil that was better than 99% pure (VPC): IR (film) 1700 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 3H), 1.12 (s, 3H), 1.16 (s, 3H), 1.52—2.18 (m, 6H), 5.05—5.18 (m, 2H), 5.84—6.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 18.0, 26.8, 27.4, 27.8, 37.4, 40.1, 45.2, 50.9, 113.5, 142.9, 217.1; exact mass, m/e 166.1356 (calcd for $C_{11}H_{18}O$, m/e 166.1357). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.31; H, 11.09.

b) Use of phosgene: The procedure for 60c was followed using pyridine (0.075 mL, 0.927 mmol); 65b (mixture of isomers, 158 mg, 0.466 mmol) in Et_2O (10 mL); $COCl_2$ (ca. 80 drops) and NaI (279 mg, 1.86 mmol) in MeCN (10 mL). Thirty min after addition of the NaI a condenser was fitted to the flask (under a stream of nitrogen). The mixture was refluxed for 45 min, cooled, evaporated, and worked up in the specified manner. The NMR spectrum (200 MHz) of the residue showed the presence of 65c (98%, using an internal standard).

2-Ethenylcyclohexanone 66c.[149]

a) The procedure for 60c was followed using Et_3N (0.20 mL, 1.44 mmol); 66b (a mixture of diastereomers, 87 mg, 0.293 mmol) in CH_2Cl_2 (2.5 mL); $MeSO_2Cl$ (101 mg, 0.878 mmol) in CH_2Cl_2 (2 mL + 0.5 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After work-up specified for 60c, the combined organic extract was dried and evaporated (good water pump vacuum) to afford 66c [53% by NMR (200 MHz) using p-iodonitrobenzene as an internal standard].

b) Use of phosgene: The procedure for 60c was followed using 66b (245 mg, 0.824 mmol), pyridine (0.12 mL, 1.48 mmol) and $COCl_2$ (ca. 80 drops) in Et_2O (10 mL) and NaI (459 mg, 3.06 mmol) in MeCN (10 mL). An NMR spectrum

(200 MHz) of the residue after work-up indicated only a trace of olefinic material.

trans-2,3-Diethenylcyclooctanone 67c.[141]

Triethylamine (1.858 g, 22.5 mmol) was injected into a stirred solution of 67b (1.569 g, 4.47 mmol) in CH_2Cl_2 (20 mL). The mixture was cooled in an ice-bath and $MeSO_2Cl$ (1.547 g, 13.5 mmol) in CH_2Cl_2 (13 mL + 2 mL rinse) was injected over 1.5 h. The ice bath was removed and, after 20 min (TLC control) the solution was shaken with a mixture of pentane (75 mL), Et_2O (75 mL) and water (25 mL). The organic phase was washed with ice-cold HCl (2% w/w, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and with brine (50 mL). The extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 x 5 cm) with 33:1 hexane—EtOAc gave material which was distilled in a Kugelrohr apparatus (64°C, 0.1 mm). Redistillation gave 67c (517 mg, 68%) as an oil, homogeneous by TLC (silica gel, 33:1 hexane—EtOAc) but of 97% purity by VPC. The compound had: IR (CCl_4) 1701 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.32—2.22 (m, 8H), 2.30—2.70 (m, 3H), 3.20 (dd, J = 11.3, 9.2 Hz, 1H), 4.93—5.20 (m, 4H), 5.47—5.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 23.4, 24.9, 27.7, 33.0, 42.3, 46.6, 59.7, 114.8, 117.1, 136.9, 141.1, 215.4; exact mass, m/e 178.1356 (calcd for $C_{12}H_{18}O$,

m/e 178.1358. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18; O, 9.10. Found: C, 80.54; H, 10.17; O, 8.91.

2-Ethenylcyclodecanone 68c.

The procedure for 61c (low R_f) was followed using Et_3N (0.33 mL, 2.36 mmol); 68b (165 mg, 0.467 mmol) in CH_2Cl_2 (5 mL); $MeSO_2Cl$ (161 mg, 1.41 mmol) in CH_2Cl_2 (4 mL + 1 mL rinse, added over 1.5 h); and an arbitrary reaction period of 10 min. After the work-up specified for 61c (low R_f) the sample was subjected to flash chromatography over silica gel (2 x 20 cm) using 30:1 hexane—EtOAc. The solvent was removed under vacuum at 20°C and the residue was distilled in a Kugelrohr apparatus (50°C, 0.01 mm) to give 68c (42 mg, 50%) as a homogeneous (TLC, silica gel, 4:1 hexane—EtOAc) oil which was pure by VPC: IR (film) 1709 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.00—2.38 (m, 14H), 2.40—2.81 (m, 2H), 3.38—3.73 (broad t d, J = 9, 2 Hz, 1H), 4.88—5.30 (m, 2H), 5.48—5.91 (m, 1H); exact mass, m/e 180.1526 (calcd for $C_{12}H_{20}O$, m/e 180.1515). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.10; H, 11.31.

When the progress of the experiment was monitored by NMR (200 MHz, internal standard) the yield of 68c was found to be ca. 91% but the compound was very sensitive to rearrangement (to the conjugated isomer). Work-up and chromatography at ca. 0°C did not improve the yield.

2-(1-Methylethenyl)-cyclohexanone 69c.[153]

a) The procedure for 60c was followed using Et_3N (0.55 mL, 3.97 mmol); 69b (mixture of diasteromers, 247 mg, 0.795 mmol) in CH_2Cl_2 (10 mL); $MeSO_2Cl$ (273 mg, 2.38 mmol) in CH_2Cl_2 (2.5 mL + 0.5 mL rinse, added over 1.5 h); and an arbitrary reaction period of 0.5 h. The acid wash used for the isolation of 60c was omitted from the work-up. The combined organic extract was dried and evaporated (good water pump vacuum) to afford 69c [62% by NMR (200 MHz), using p-iodonitrobenzene as an internal standard; 91% after correction for starting material[154] (78.3 mg, 31%) recovered by flash chromatography of the NMR sample over silica gel (2 x 15 cm) with 4:1 heptane—EtOAc].

For characterization of 69c the experiment was repeated on almost the same scale and the reaction mixture was poured into pentane—Et_2O and washed as described for 63c (low R_f). The organic phase was dried and evaporated and the residue was chromatographed over silica gel impregnated with 5% w/w $AgNO_3$ (1 x 35 cm) using 5:1 hexane—EtOAc. Kugelrohr distillation (bp 30°C, 0.01 mm) then afforded 69c as a homogeneous (TLC, silica gel impregnated with 5% w/w $AgNO_3$, 5:1 hexane—EtOAc) oil: IR (film) 1710 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.54—2.20 (m, including a singlet broadened by unresolved coupling at δ 1.77, 9H), 2.24—2.54 (m, 2H), 3.04 (dd, J = 11.3, 5.4 Hz, 1H), 4.70—4.82

(m, 1H), 4.90—5.03 (m, 1H); exact mass, m/e 138.1046 (calcd for $C_9H_{14}O$, m/e 138.1045). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.12; H, 10.16.

b) Use of phosgene: The procedure for 60c was followed using 69b (199 mg, 0.639 mmol), pyridine (0.10 mL, 1.28 mmol) and $COCl_2$ (ca. 80 drops) in Et_2O (10 mL) and NaI (192 mg, 1.28 mmol) in MeCN (10 mL). An NMR spectrum (200 MHz) of the residue after work-up indicated only a trace of 69c.

1,2-Diethenyl-2-methylcyclohexanol 60d and 60d'.

Vinylmagnesium bromide (0.92 M in THF, 6.10 mL, 5.61 mmol) was injected over ca. 2 min into a stirred solution of 60c (380 mg, 2.75 mmol) in THF (10 mL) at -30°C. The cold bath was then removed and, after an arbitrary period of 30 min, the reaction mixture was partitioned between 2:1 pentane—Et_2O (75 mL) and ice-cold aqueous HCl (2% w/w, 50 mL). The aqueous layer was extracted with Et_2O (25 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and with brine (50 mL) and was then dried. Evaporation of the extract and Kugelrohr distillation (bp 94°C, 3 mm) gave the product (320 mg, 70%) as a mixture of isomers. Chromatography over silica gel impregnated with 5% w/w $AgNO_3$ (2 x 70 cm) using 1:4 hexane—EtOAc afforded 51 mg of low R_f material.

The other isomer from the silica gel $AgNO_3$ column was rechromatographed over silica gel (1 x 25 cm) using 8:1 hexane—EtOAc to yield 170 mg of high R_f product.

60d: Low R_f compound: IR (film) 3470, 3080, 3020, 1634 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.08 (s, 3H), 1.18—1.34 (m, 1H), 1.36—2.01 (m, 8H), 4.97—5.33 (m, 4H), 5.89—6.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.1, 21.3, 21.8, 32.0, 33.4, 43.2, 75.0, 113.1, 114.5, 142.5, 144.8; exact mass, m/e 166.1356 (calcd for $C_{11}H_{18}O$, m/e 166.1358). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.47; H, 10.85.

60d': High R_f compound: IR (film) 3480, 3080, 3020, 1633 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.03 (s, 3H), 1.35—1.80 (m, 9H), 4.96—5.33 (m, 4H), 6.03—6.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 20.1, 21.2, 21.8, 34.6, 34.8, 43.3, 75.4, 112.7, 113.2, 142.9, 143.9; exact mass, m/e 166.1362 (calcd for $C_{11}H_{18}O$, m/e 166.1358). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.44; H, 10.70.

6-Methylcyclodec-5-enone 60e.[52c]

a) Potassium hydride (24.01% w/w in oil, 131 mg, 0.787 mmol) was washed in a septum covered flask with dry pentane (2 x 5 mL). Residual solvent was evaporated by a stream of nitrogen and THF (5 mL) was added to the flask. The alcohol 60d' (high R_f material, 109 mg, 0.656 mmol) in THF (4 mL + 1 mL rinse) was then injected and the mixture

was stirred at room temperature until evolution of hydrogen ceased (ca. 15 min). The flask was purged with nitrogen while a condenser was fitted and the mixture was refluxed for 15 min. It was then partitioned between pentane (50 mL) and aqueous NH_4Cl (10% w/w, 50 mL) and the aqueous layer was extracted with Et_2O (50 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and with brine (50 mL) and was then dried. Evaporation of the solvent and Kugelrohr distillation of the residue (bp 90°C, 0.05 mm) gave 60e (104 mg, 95%) better than 97% pure (VPC). Two isomers (ca. 1:8.6)[151] were present, as judged by VPC—mass spectral analysis. They were not separated by TLC (silica gel impregnated with 5% w/w $AgNO_3$, 4:1 hexane—EtOAc). The mixture had: IR (film) 1704 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.45—2.21 (m, including a doublet at 1.73, J = 1.2 Hz, 15H), 2.27—2.51 (m, 2H), 4.89—5.05 (m, 0.9H), 5.08—5.21 (m, 0.1H); ^{13}C ($CDCl_3$, 50.32 MHz) δ 16.0, 22.5, 25.2, 28.3, 28.4, 40.2, 42.5, 43.5, 129.2, 134.6, 212.5; exact mass, m/e 166.1356 (calcd for $C_{11}H_{18}O$, m/e 166.1357). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.32; H, 11.09.

The minor isomer, 60e', showed a multiplet at δ 5.14 and a broad singlet at δ 1.65 in its 200 MHz NMR spectrum corresponding to the vinyl and methyl signals, respectively. The corresponding signals for the major

isomer were at δ 4.97 and δ 1.73. Irradiation at δ 1.65 caused enhancement of the multiplet at δ 5.14, while irradiation at δ 1.73 produced no noticeable enhancement of the multiplet at δ 4.97. This NOE experiment establishes the double bond geometry as E for the major isomer and Z for the minor. The major isomer was identical to an authentic specimen[155] of (5-E)-6-methylcyclodec-5-enone.

b) The above oxy-Cope rearrangement was repeated using 60d (low R_f material, 27.5 mg, 0.166 mmol) in THF (2 mL + 1 mL rinse) and KH (24.01% w/w in oil, 33.2 mg, 0.199 mmol) in THF (5 mL). Work-up and Kugelrohr distillation gave 60e (23.3 mg, 84%) of better than 99% purity (VPC). This material was the (E) isomer[155] and had: IR (film) 1701 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.49—2.27 (m, including a doublet at 1.73, J = 1.5 Hz, 15H), 2.29—2.47 (m, 1H), 4.88—5.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 16.0, 22.5, 25.2, 28.3, 28.4, 40.2, 42.5, 43.5, 129.2, 134.7, 212.5; exact mass, m/e 166.1356 (calcd for $C_{11}H_{18}O$, m/e 166.1357).

(E,E)-Cyclododeca-2,6-dienone 67d.[141]

trans-2,3-Diethenylcyclooctanone 67c (150.5 mg, 0.8 mmol) in biphenyl (913 mg) was heated under nitrogen for 20 min in a preheated oil bath at 200°C. The resulting

mixture was applied with the aid of a little hexane to a silica gel column (2 x 22 cm) made up in hexane. Elution with 19:1 hexane—EtOAc gave 67d (135 mg, 90%) as a homogeneous (TLC, silica gel impregnated with 15% w/w $AgNO_3$, 4:1 hexane—EtOAc oil that solidified on cooling: mp 35—36°C; IR(CCl_4) 1695 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.10—2.25 (m, 2H), 1.35—1.52 (m, 2H), 1.52—1.70 (m, 2H), 2.00—2.18 (m, 2H), 2.18—2.34 (m, 4H), 2.34—2.46 (m, 2H), 5.0—5.2 [m, incorporating a ^3J = ca. 15 Hz (observed by decoupling experiments), 2H], 6.11 (d, J = 14 Hz, 1H), 6.3—6.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 23.1, 24.4, 26.3, 30.3, 31.5, 31.9, 42.5, 130.5, 132.0, 132.3, 144.2, 203.0; exact mass, m/e 179.1356 (calcd for $C_{12}H_{18}O$, m/e 178.1358). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.81; H, 10.32.

1-Dodecene.

The procedure for 60c was followed using 83[147] (186 mg, 0.545 mmol), pyridine (0.09 mL, 1.11 mmol) and $COCl_2$ (ca. 80 drops) in Et_2O (10 mL) and NaI (163 mg, 1.09 mmol) in MeCN (10 mL). After addition of the NaI the mixture was refluxed for 30 min and then worked-up in the usual manner. The NMR spectrum (200 MHz) of the residue showed the presence of 1-dodecene[120] (61%, using an internal standard).

Attempted Cope Rearrangement of 63c.

trans-2-(Ethenyl)-3-(1-methylethenyl)cyclohexanone 63c (78.0 mg, 0.475 mmol) was placed in a 5 mL round bottomed flask containing biphenyl (300 mg, 1.95 mmol). The flask was fitted with a condenser and the apparatus was purged with nitrogen prior to immersion in a preheated oil bath (200°C). Since only minor changes were evident in the mixture (VPC control) after 20 min, the oil bath temperature was raised to 265°C. After 1 h (VPC control) the mixture was cooled and flash chromatographed over silica gel (2 x 15 cm) with 10:1 heptane—EtOAc. The eluant was then filtered through a column (1 x 15 cm) of silica gel impregnated with 5% w/w $AgNO_3$ with 4:1 heptane—EtOAc to give 63d' (33.9 mg, 0.206 mmol) and 63d (7.9 mg, 0.048 mmol) after Kugelrohr distillation: 63d (bp 78°C, 0.03 mm) 100% pure by VPC; IR (film) 1687 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.62—2.08 (m, including a doublet at δ 1.69, J = 7.6 Hz and a singlet at δ 1.80 split by unresolved coupling, 10H), 2.17—2.59 (m, 2H), 3.42—3.54 (m, 1H), 4.50—4.59 (m, 1H), 4.82—4.90 (m, 1H), 6.82 (qd, J = 7.2, 1.2 Hz, 1H); exact mass, m/e 164.1202 (calcd for $C_{11}H_{16}O$, m/e 164.1201). 63d' (bp 78°C, 0.03 mm) >99% pure by VPC (94.5% one isomer, 5.1% of the above isomer); IR ($CDCl_3$) 1687 cm^{-1}; NMR ($CDCl_3$, 200 MHz), 1.66—2.14 (m, including a singlet at δ 1.72 split by

unresolved coupling, and a dd at δ 1.93, J = 7.2, 1.2 Hz, 10H), 2.24—2.58 (m, 2H), 3.10—3.24 (m, 1H), 4.63—4.72 (m, 1H), 4.88—4.97 (m, 1H), 5.73 (qd, J = 7.2, 1.1 Hz, 1H); exact mass, m/e 164.1199 (calcd for $C_{11}H_{16}O$, m/e 164.1201).

2-(1-Hydroxy-2-phenylselenoethyl)-6-methylcyclodec-5-enone

78.[156]

Potassium hydride (24.01% in oil, 110 mg, 0.661 mmol) was washed in a septum covered flask with dry pentane (2 x 5 mL). Residual solvent was evaporated by a stream of nitrogen and THF (5 mL) was added to the flask. A mixture of alcohols 60d' and 60d (2.1:1 VPC, 100 mg, 0.602 mmol) in THF (4 mL + 1 mL rinse) was then injected and the mixture was stirred at room temperature until evolution of hydrogen ceased (ca. 15 min). The flask was purged with nitrogen while a condenser was fitted and the mixture was refluxed for 15 min. The solution was cooled to 0°C and $ZnCl_2$ (0.80 mL of a saturated Et_2O solution, 0.552 mmol) was added dropwise. The solution was stirred for 5 min at 0°C and phenylselenoacetaldehyde (110 mg, 0.552 mmol) in THF (4 mL + 1 mL rinse) was injected rapidly. The mixture was stirred for an additional 5 min and was then poured into a flask containing pentane (100 mL) and aqueous NH_4Cl (10% w/w, 50 mL). The aqueous phase was

further extracted with Et_2O (20 mL) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The solution was dried and evaporated, resulting in a residue which was flash chromatographed over silica gel (2 x 20 cm) with 8:1 heptane—EtOAc to give 78 as two apparently homogeneous (TLC, silica gel, 8:1 heptane—EtOAc) selenides of combined weight 128 mg (63%). The material of higher R_f (55.2 mg, 27%) was an oil: IR ($CDCl_3$) 1700 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.32—2.70 (m, 16H), 2.73—3.21 (m, 3H), 3.52—3.67 (m, 1H), 4.80—5.01 (m, 1H), 7.14—7.32 (m, 3H), 7.40—7.58 (m, 2H); exact mass, m/e 366.1101 (calcd for $C_{19}H_{26}O_2{}^{80}Se$, m/e 366.1098). Anal. Calcd for $C_{19}H_{26}O_2Se$: C, 62.46; H, 7.17; O, 8.76. Found: C, 62.60; H, 7.40; O, 8.97.

The material of lower R_f (73.0 mg, 36%) was an oil: IR ($CDCl_3$) 1698 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.32—2.66 (m, 16H), 2.76—3.16 (m, 3H), 3.47—3.66 (m, 0.64H), 3.80—4.02 (m, 0.36H), 4.80—4.96 (m, 0.64H), 5.00—5.14 (m, 1H), 7.14—7.34 (m, 3H), 7.37—7.57 (m, 2H); exact mass, m/e 366.1095 (calcd for $C_{19}H_{26}O_2{}^{80}Se$, m/e 366.1098). Anal. Calcd for $C_{19}H_{26}O_2Se$: C, 62.46; H, 7.17; O, 8.76. Found: C, 62.75; H, 7.25; O, 8.43.

In addition to the selenides, a mixture of 60e' and 60e was also recovered from the flash chromatography. The mixture was further purified by PLC chromatography

over silica gel with 4:1 heptane—EtOAc to give 60e and 60e' (24:1 by VPC, 27.1 mg) after Kugelrohr distillation.

2-(1-Hydroxy-2-phenylselenoethyl)cyclohexadec-5-enone 80.[91]

Diisopropylamine (22.1 mg, 0.218 mmol) in THF (1 mL + 0.5 mL rinse) was added to a stirred solution of tert-potassium butoxide (24.5 mg, 0.218 mmol) in THF (2 mL) at -78°C. The mixture was stirred for 5 min and butyllithium (0.135 mL, 1.61 M hexane solution, 0.218 mmol) was added dropwise over 2 min. The mixture was then stirred for 15 min at -78°C and the alcohol 79[89] (51.6 mg, 0.218 mmol) in THF (1 mL + 0.5 mL rinse) was added. After an additional 15 min stir period at -78°C the cold bath was removed and the solution was warmed to room temperature over 15 min. Subsequent refluxing for 15 min and cooling to 0°C was followed by addition of $ZnCl_2$ (0.316 mL, saturated Et_2O solution, 0.218 mmol). After 5 min a solution of phenylselenoacetaldehyde (43.5 mg, 0.218 mmol) in THF (1.5 mL + 0.5 mL rinse) was added over ca. 3 sec and the mixture was stirred for another 5 min. The solution was then poured into pentane (25 mL) and aqueous NH_4Cl (10%, 25 mL). After the mixture had been shaken in a separatory funnel the aqueous layer was separated and extracted with Et_2O (2 x 20 mL). The

combined organic fractions were washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL) and were then dried. Evaporation of the solvent left a pale yellow residue which was purified by flash chromatography over silica gel (2 x 9 cm) with 4:1 heptane—EtOAc to give $\underline{80}^{91}$ (81.8 mg, 86%) as a mixture of diastereoisomers (two spots by TLC, silica gel, 4:1 heptane—EtOAc): IR (film) 1706 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.11—2.18 (m, 22H), 2.20—2.60 (m, 2H), 2.86—3.18 (m, 3H), 2.83 (d, J = 3 Hz), 3.48 (d, J = 8 Hz), 3.54 (d, J = 4 Hz) total integration = 1H, 3.69—3.96 (m, 1H), 5.19—5.49 (m, 2H), 7.19—7.35 (m, 3H), 7.43—7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 15.3, 22.1, 22.4, 25.6, 25.9, 26.0, 26.1, 26.2, 26.3, 26.6, 26.9, 27.1, 27.2, 28.0, 29.6, 30.1, 31.6, 31.7, 33.6, 34.0, 42.8, 43.1, 52.6, 53.7, 65.8, 70.5, 70.9, 76.4, 77.2, 127.4, 129.2, 129.3, 129.5, 132.1, 132.5, 133.0, 214.4, 216.5; exact mass, m/e 436.1879 (calcd for $C_{24}H_{36}O_2{}^{80}Se$, m/e 436.1880). Anal. Calcd for $C_{24}H_{36}O_2Se$: C, 66.19; H, 8.33; O, 7.35. Found: C, 66.49; H, 8.50; O, 7.68.

NOTES AND REFERENCES

1. a) Clive, D.L.J. Tetrahedron 1978, 34, 1049; b) Clive, D.L.J. Aldrichimica Acta 1978, 11, 43; c) Sharpless, K.B.; Gordon, K.M.; Lauer, R.F.; Patrick, D.W.; Singer, S.P.; Young, M.W. Chemica Scripta 1975, 8A, 9; d) Reich, H.J. Acc. Chem. Res. 1979, 12, 22; e) Reich, H.J. In "Oxidation in Organic Chemistry, Part C", Trahanovsky, W. Ed., Academic Press, New York, 1978, p 1.
2. Klayman, D.L.; Günther, W.H.H., Eds.; "Organic Selenium Compounds: Their Chemistry and Biology", Wiley-Interscience: New York, 1973.
3. Grieco, P.A. Synthesis 1975, 67.
4. a) Rao, Y.S. Chem. Rev. 1976, 76, 625; b) Newaz, S.S. Aldrichimica Acta 1977, 10, 64.
5. a) Masamune, S. Ibid. 1978, 11, 23; b) Masamune, S.; Bates, G.S.; and (in part) Corcoran, J.W. Angew. Chem. Int. Ed. Engl. 1977, 16, 585; c) Back, T.G. Tetrahedron 1977, 33, 3041; d) Nicolaou, K.C. Ibid. 1977, 33, 683.
6. a) Corey, E.J.; Gross, A.W. Tetrahedron Lett. 1980, 1819; b) Moriarty, R.M.; Walsh, H.G.; Gopal H. Ibid. 1966, 4363.
7. a) Senda, Y.; Kamiyama, S.; Imaizumi, S. J. Chem. Soc. Perkin Trans. 1 1978, 530 and references therein;

b) Factor, A.; Traylor, T.G. J. Org. Chem. 1968, 33, 2607; c) Rowland, R.L.; Perry, W.L.; Friedman, H.L. J. Am. Chem. Soc. 1951, 73, 1040.

8. a) Davies, D.I.; Dowle, M.D. J. Chem. Soc. Perkin Trans. 1 1978, 227; b) Ansell, M.F.; Palmer, M.H. J. Chem. Soc. 1963, 2640; c) Klein, J. J. Org. Chem. 1958, 23, 1209.
9. Dowle, M.D.; Davies, D.I. Chem. Soc. Rev. 1979, 8, 171.
10. Whitlock Jr., H.W. J. Am. Chem. Soc. 1962, 84, 3412.
11. Still, W.C.; Schneider, M.J. Ibid. 1977, 99, 948.
12. While haloactonization has been performed in organic solvents, yields of the lactonic products are usually poor due to the formation of dihalo acids; see reference 9.
13. de Moura Campos, M.; Petragnani, N. Chem. Ber. 1960, 93, 317.
14. Berti, G. Tetrahedron 1958, 4, 393.
15. Clive, D.L.J. J. Chem. Soc., Chem. Comm. 1973, 695.
16. a) Sharpless, K.B.; Young, M.W., Lauer, R.F. Tetrahedron Lett. 1973, 1979; b) Reich, H.J.; Renga, J.M.; Reich, I.L. J. Am. Chem. Soc. 1975, 97, 5434.
17. Johnson, R.A.; Lincoln, F.H.; Thompson, J.L.; Nidy, E.G.; Mizsak, S.A.; Axen, U. Ibid. 1977, 99, 4182.

18. Corey, E.J.; Keck, G.E.; Székely, I. Ibid. 1977, 99, 2006.

19. Clive, D.L.J.; Chittattu, G.J.; Farina, V.; Kiel, W.A.; Menchen, S.M.; Russell, C.G.; Singh, A.; Wong, C.W.; Curtis, N.J. Ibid. 1980, 102, 4438.

20. This reagent is commercially available.

21. Defined as a process in which one terminus of the double bond involved in the intramolecular ring closure becomes attached to a group that allows futher modification at that site; see: Clive, D.L.J.; Chittattu, G.; Curtis, N.J.; Kiel, W.A.; Wong, C.K. J. Chem. Soc., Chem. Commun. 1977, 725.

22. a) Clive, D.L.J.; Russell, C.G.; Chittattu, G.; Singh, A. Tetrahedron, 1980, 36, 1399; b) Clive, D.L.J.; Chittattu, G. J. Chem. Soc., Chem. Commun. 1977, 484; c) Nicolaou, K.C.; Seitz, S.P.; Sipio, W.J.; Blount, J.F. J. Am. Chem. Soc. 1979, 101, 3884.

23. For recent applications see: a) Danishefsky, S.; Funk, R.L.; Kerwin Jr., J.F. Ibid. 1980, 102, 6889; b) Baldwin, J.E.; Reed, N.V.; Thomas, E.J. Tetrahedron 1981, 37, 263.

24. This catalytic effect of silica gel has been observed previously, see: a) Clive, D.L.J.; Farina, V.; Singh, A.; and (in part) Wong, C.K.; Kiel, W.A.; Menchen, S.M. J. Org. Chem. 1980, 45, 2120; b) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. Tetrahedron Lett. 1979, 4801.

25. For discussion of this aspect see: a) House, H.O.; Carlson, R.G.; Babad, H. J. Org. Chem. 1963, 28, 3359; b) Julia, M.; LeGoffic, F. Bull. Soc. Chim Fr. 1965, 1555; see also reference 9.

26. Herz, W.; Glick, L.A. J. Org. Chem. 1963, 28, 2970.

27. Baldwin, J.E. J. Chem. Soc., Chem. Commun. 1976, 734.

28. Singer, H.; Unpleby, J.D. Tetrahedron 1972, 28, 5769.

29. Reich, H.J.; Renga, J.M. J. Org. Chem. 1975, 40, 3313.

30. Behaghel, O.; Seibert, H. Chem. Ber. 1933, 66, 708.

31. Lawson, D.D.; Kharasch, N. J. Org. Chem. 1959, 24, 859.

32. Similar results were observed when benzeneselenenyl chloride was added to the methyl ester 18. For discussions of similar observations see: Raucher, S. Ibid. 1977, 42, 2950; and Liotta, D.; Zima, G. Tetrahedron Lett. 1978, 4977. For a similar observation with sulfur moieties see: Hogg, D.R.; Beverly, G.M. J. Chem. Soc., Chem. Commun. 1966, 138.

33. a) Sharpless, K.B.; Lauer, R.F. J. Org. Chem. 1974, 39, 429; b) Garratt, D.G., Schmid, G.H. Can. J. Chem. 1974, 52, 3599; c) Jenny, W. Helv. Chim. Acta 1958 41, 593 and references therein; d) Reich, H.J. J. Org. Chem. 1974, 39, 428; e) Cook, W.S.; Donia, R.A. J. Am. Chem. Soc. 1951, 73, 2275; f) Behagel, O.; Müller, W. Chem. Ber. 1935, 68, 1540.

34. Bell, P.A.; Hogg, D.R.; Robertson, A. J. Chem. Soc. Perkin Trans. 1 1978, 1246 and references therein.

35. This decomposition was confirmed for the reaction of sodium-4-pentenoate with phenylsulfenyl chloride. Although the products were not isolated, solution IR spectra indicated bands at 1710, 1740, 1760, and 1788 cm^{-1}.

36. Putman, R.E.; Sharkey, W.H. J. Am. Chem. Soc. 1957, 79, 6526.

37. There is confusion in the literature concerning the authenticity of some of these compounds, see references 33e and 33f.

38. Reich has reported an $IR_{\nu C=O}$ value of 1727 cm^{-1} for CF_3CO_2SePh in CH_2Cl_2, see reference 33d.

39. a) Schmid, G.H.; Garratt, D.G. Tetrahedron Lett. 1975, 3991; b) Reich, H.J.; Trend, J.E. Can. J. Chem. 1975, 53, 1922; c) Schmid, G.H.; Garratt, D.G. In "The Chemistry of Functional Groups. Supplement A. The Chemistry of Double-Bonded Functional Groups." Patai, S., Ed.; Wiley and Sons: London, 1977, pp. 855-866.

40. For a similar example using halolactonization see reference 14.

41. Sharpless, K.B.; Current, S. Tetrahedron Lett. 1978, 5075; see also reference 21.

42. Stork, G.; Cohen, J.F. J. Am. Chem. Soc. 1974, 96, 5270.

43. Intermediates in the postulated scheme were not isolated.

44. For oxidation of hydrazides with $PhSeO_2H$ see: Back, T.G. J. Chem. Soc., Chem. Commun. 1978, 278.

45. Do Amaral, L.; Melo, S.C. J. Org. Chem. 1973, 38, 800.

46. For recent interest in modes of cyclization see: a) Danishefsky, S. Acc. Chem. Res. 1979, 12, 66; b) Trost, B.M.; Verhoeven, T.R. J. Am. Chem. Soc. 1979, 101, 1595.

47. a) Taber, D.F.; Saleh, S.A.; Korsmeyer, R.W., J. Org. Chem. 1980, 45, 4699; b) Neumann, H.; Seebach, D. Tetrahedron Lett. 1976, 4839; c) Schmidt, R.R.; Talbiersky, J.; Russegger, P. Ibid. 1979, 4273; d) Derguini-Boumechal, F.; Linstrumelle, G. Ibid. 1976, 3225 and references therein; e) Eisch, J.J.; Damasevitz, G.A. J. Org. Chem. 1976, 41, 2214; f) Baba, S.; Van Horn, D.E.; Negishi, E. Tetrahedron Lett. 1976, 1927.

48. The preparative use of such a moiety could facilitate the synthesis of a large number of natural products. For examples see: a) Kupchan, S.M.; Hemingway, R.J.; Werner, D.; Karim, A.; McPhail, A.T.; Sim, G.A. J. Am. Chem. Soc. 1968, 90, 3596; b) Battersby, A.R.; Burnett, A.R.; Knowles, G.D.; Parson, P.G. J. Chem. Soc., Chem. Commun. 1968, 1277; c) Inouye, H.;

Ueda, S.; Nakamura, Y. Tetrahedron Lett. 1966, 5229; d) Thomas, R. Ibid. 1961, 544.

49. For reviews on vinyl cations see: a) Hanack, M. Angew. Chem. Int. Ed. Engl. 1978, 17, 333; b) Stang, P.J. Acc. Chem. Res. 1978, 11, 107.

50. For a recent review see: a) Heimgartner, H. Chimia 1980, 34, 333; see also: b) Fehr, C.; Ohloff, G.; Büchi, G., Helv. Chim. Acta 1979, 62, 2655; c) Büchi, G.; Wüest, H. Ibid. 1979, 62, 2661; d) Schulte-Elte, K.H.; Hauser, A.; Ohloff, G. Ibid. 1979, 62, 2673; e) Trost, B.M.; Vincent, J.E. J. Am. Chem. Soc., 1980, 102, 5680.

51. a) Rhoads, S.J.; Raulins, N.R. In "Organic Reactions", Dauben, W.G., Ed.; John Wiley and Sons, Inc.: New York, 1975; Vol. 22, Chapter 1; b) Evans, D.A.; Baillargeon, D.J.; Nelson, J.V. J. Am. Chem. Soc. 1978, 100, 2242 and references therein.

52. a) Berson, J.A.; Gajewski, J.J. Ibid, 1964, 86, 5019; b) Seebach, D.; Geiss, K.; Pohmakotr, M. Angew. Chem. Int. Ed. Engl. 1976, 15, 437; c) Evans, D.A.; Golob, A.M. J. Am. Chem. Soc. 1975, 97, 4765; d) Evans, D.A.; Nelson, J.V. Ibid. 1980, 102, 774; e) Still, W.C. Ibid. 1977, 99, 4186.

53. a) Ziegler, F.E.; Piwinski, J.J. Ibid. 1980, 102, 880; b) Ibid. 1979, 101, 1612; c) Raucher, S.; Burks Jr., J.E.; Hwang, K.; Svedberg, D.P. Ibid, 1981, 103, 1853.

54. Recently a method for an eight unit ring expansion has been reported, see: Wender, P.A.; Sieburth, S. McN. Tetrahedron Lett. 1981, 2471.

55. Structures do not have any stereochemical implications.

56. Kato, T.; Kondo, H.; Nishino, M.; Tanaka, M.; Hata, G.; Miyake, A. Bull. Chem. Soc. Jpn. 1980, 53, 2958.

57. Watanabe, S.; Suga, K., Fujita, T.; Gomi, T. J. Appl. Chem. Biotechnol. 1973, 23, 501.

58. Procedures based on Michael addition to phenylvinylsulfoxide: a) Koppel, G.A.; Kinnick, M.D. J. Chem. Soc., Chem. Commun. 1975, 473; b) Bruhn, J.; Heimgartner, H.; Schmid, H. Helv. Chim. Acta 1979, 62, 2630; Procedure based on Michael addition to a vinyl sulfone: c) Metcalf, B.W.; Bonilavri, E. J. Chem. Soc., Chem. Commun. 1978, 914; Transition metal catalyzed vinylation: d) Rathke, M.W.; Millard, A.A. J. Am. Chem. Soc. 1977, 99, 4833; e) Hudrlik, P.F.; Hudrlik, A.M.; Rona, R.J.; Misra, R.N.; Withers, G.P. Ibid. 1977, 99, 1993; f) Eisch, J.J.; Galle, J.E. J. Org. Chem. 1976, 41, 2615; g) Chang, T.C.T.; Rosenblum, M.; Samuels, S.B. J. Am. Chem. Soc. 1980, 102, 5930.

59. The preparation of 54 proved to be a difficult task in this laboratory, resulting in low yields of the reagent.

60. a) Peterson, D.J. J. Org. Chem. 1968, 32, 780;
b) Colvin, E.W. Chem. Soc. Rev. 1978, 7, 15.

61. Cadogan, J.I.G.; Ed.; "Organophosphorus Reagents in Organic Synthesis", Academic Press: New York, 1979.

62. Baudat, R.; Petrzilka, M. Helv. Chim. Acta 1979, 62, 1406.

63. a) House, H.O.; Crumrine, D.S.; Teranishi, A.Y.; Olmstead, H.D. J. Am. Chem. Soc. 1973, 95, 3310;
b) Heng, K.K.; Smith, R.A.J. Tetrahedron 1979, 425.

64. a) Stork, G.; Hudrlik, P.F. J. Am. Chem. Soc. 1968, 90, 4464; see also: b) Fleming, I. Chimia 1980, 34, 265; c) Rasmussen, J.K. Synthesis 1977, 91.

65. a) Mukaiyama, T.; Inoue, T. Chem. Lett. 1976, 559;
b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. Ibid. 1977, 153; c) Inoue, T.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 1980, 53, 174; d) Hirama, M.; Masamune, S. Tetrahedron Lett. 1979, 2225; e) Van Horn, D.E.; Masamune, S. Ibid. 1979, 2229; f) Hirama, M.; Garvey, D.S.; Lu, L.D.-L.; Masamune, S. Ibid, 1979, 3937; g) Evans, D.A.; Bartroli, J. Shih, T.L. J. Am. Chem. Soc. 1981, 103, 2127; h) Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. Ibid. 1981, 103, 3099.

66. For a detailed discussion of enolates see: d'Angelo, J. Tetrahedron 1976, 32, 2979.

67. a) Näf, F.; Decorzant, R. Helv. Chim. Acta 1974, 57, 1317; see also: reference 66 and reference 63a.

68. a) Camus, A.; Diara, A.; Damiano, J.-C. C.R. Acad. Sci., Ser. C 1975, 280, 523; b) Mookherjee, B.D.; Trenkle, R.W.; Patel, R.R. J. Org. Chem. 1971, 36, 3266; c) Mookherjee, B.D.; Patel, R.R.; Ledig, W.O. Ibid. 1971, 36, 4124. For effect of solvent see: d) House, H.O.; Respess, W.L.; Whitesides, G.M. Ibid. 1966, 31, 3128.

69. Hooz, J.; Mortimer, R.D. Can. J. Chem. 1978, 56, 2786.

70. Usually one isomer did react a little faster (TLC control) than the other.

71. For example: 63b (High R_f), 63b (Low R_f) and 67b contained less than 1% of the corresponding cis isomer; 62b (High R_f) contained less than 2%.

72. Preparation: a) Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. J. Am. Chem. Soc. 1973, 95, 6137; b) Ryu, I.; Murai, S.; Niva, I.; Sonoda, N. Synthesis 1977, 874.

73. Condensations between ketones usually give poor yields of the aldol product due to unfavorable equilibria or subsequent dehydration to the unsaturated ketone, see: House, H.O. "Modern Synthetic Reactions" 2nd Ed.; W.A. Benjamin Inc.: Don Mills, Ontario, 1972, pp 629.

74. This synthon is particularly adapt for the synthesis of sesquiterpenes, for examples see: a) Bonner, W.A.; Burke, N.I.; Fleck, W.E.; Hill, R.K.; Joule, J.A.; Sjöberg, B.; Zalkow, J.H. Tetrahedron 1964, 20, 1419; b) Ehret, C.; Ourisson, G. Ibid. 1969, 25, 1785.

75. Rémion, J.; Krief, A. Tetrahedron Lett. 1976, 3743.

76. Reich, H.J.; Chow. F. J. Chem. Soc., Chem. Commun. 1975, 790.

77. For a similar approach see: Rémion, J.; Dumont, W.; Krief, A. Tetrahedron Lett. 1976, 1385.

78. Mukaiyama, T.; Imaoka, M. Chem. Lett. 1978, 413.

79. The addition of the methanesulfonyl chloride can be carried out at 0°C provided that the reaction mixture is allowed to stir at room temperature for a period of time prior to work-up.

80. Reich, H.J.; Chow, F.; Shah, S.K. J. Am. Chem. Soc. 1979, 101, 6638.

81. For reviews see: a) King, J.F. Acc. Chem. Res. 1975, 8, 10 and references therein; b) Opitz, G. Angew. Chem. Int. Ed. Engl. 1967, 6, 107.

82. Chloroformate review: Mätzner, M.; Kurkjy, R.P.; Cotter, R.J. Chem. Rev. 1964, 64, 645.

83. a) Barton, D.H.R.; McCombie, S.W. J. Chem. Soc., Perkin Trans. 1 1975, 1574; b) Kevill, D.N.; Weitl, F.L. J. Org. Chem. 1967, 32, 2633.

84. 2-Ethenylcyclododecanone is far less sensitive in this respect. Preparation: (1-cyclododecen-1-yloxy)-trimethylsilane → 2-(1-hydroxy-2-phenylselenoethyl)-cyclododecanone (ca. 87%) → 2-ethenylcyclododecanone (ca. 77%).

85. a) The boat-chair conformation shown for the eight-membered ring is a tentative assignment and the conformation (excluding the olefin geometry) of the twelve-membered ring is arbitrary; b) For discussions of the conformational analysis of medium and large rings see: Dale, J. "Stereochemistry and Conformational Analysis", Verlag Chemie: New York, 1978.

86. a) Marvell, E.N.; Whalley, W. Tetrahedron Lett. 1970, 509; b) The conformation shown for 60e is tentative, that shown for 60e' is arbitrary (see reference 85b).

87. Eliel, E.L. "Stereochemistry of Carbon Compounds", McGraw-Hill Book Co. Inc.: Toronto, 1962.

88. The conformations shown are arbitrary.

89. This alcohol was prepared by Dr. S. Suri using a sequence similar to that used for the alcohols 60d and 60d'. In the final step vinyllithium[47a] was used to prepare the divinyl alcohol instead of vinylmagnesium bromide (overall yield, 60%). The alcohol was a mixture of isomers (1:2.3, cis:trans) and was completely characterized.

90. Raucher, S.; Koolpe, G.A. J. Org. Chem. 1978, 43, 3794.

91. As with compound 78 , spectral data for 80 was not exceptional. Therefore the presence of the alternative regioisomer of 80 cannot be dismissed at this time.

92. For preparative details see end of experimental section.

93. For published results of this work see: a) Clive, D.L.J.; Russell, C.G. J. Chem. Soc., Chem. Commun. 1981, 434; see also: b) Kowalski, C.J.; Dung, J.-S. J. Am. Chem. Soc. 1980, 102, 7950.

94. Thies, R.W. Ibid. 1972, 94, 7074.

95. An American supplier of this BASF catalyst is Chemical Dynamics Corp. Hadley Industrial Plaza, P.O. Box 395, South Plain Field, N.J. 07080.

96. 100% "Punctilious" ethanol was used without further drying. Supplier: United States Industrial Chemicals Co., Division of the National Distillers and Chemical Corp., New York, New York, 10016.

97. This experiment was performed by Dr. G. Chittattu.

98. Linstead, R.P.; Rydon, H.N. J. Chem. Soc. 1933, 580.

99. Fieser, M.; Fieser, L.F. "Reagents for Organic Synthesis", Vol. 5, John Wiley and Sons: Toronto, 1975, p 523.

100. Prepared in the same manner as for sodium-4-pentenoate.

101. Fetizon, M.; Golfier, M.; Montaufier, M.T.; Rens, J. Tetrahedron 1975, 31, 987.

102. Kuivila, H.G.; Beumel Jr., O.F. J. Am. Chem. Soc. 1961, 83, 1246.

103. Jäger, V.; Günther, H.J. Tetrahedron Lett. 1977, 2543.

104. Crombie, L.; Edgar, A.J.B.; Harper, S.H.; Lowe, M.W.; Thompson, D. J. Chem. Soc. 1950, 3552.

105. NMR indicated the presence of approximately 10% of 4-methyl-3-pentenoic acid as an impurity in the starting material.

106. Marshall, H.; Vogel, F.; Weyerstahl, P. Justus Liebigs Ann. Chem. 1977, 9, 1557.

107. a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Ferrell, R. J. Am. Chem. Soc. 1963, 85, 207; b) Monson, R.S. "Advanced Organic Synthesis, Methods and Techniques", Academic Press: New York, 1971, p. 84.

108. Boehme, W.R.; Schipper, E.; Scharpf, W.G.; Nicols, J. J. Am. Chem. Soc. 1958, 80, 5488.

109. This experiment was performed by Dr. A. Singh.

110. Whitlock Jr., H.W. Ibid. 1962, 84, 3412.

111. DeTar, D.F.; Carpino, L.A. Ibid. 1956, 78, 475.

112. Leupold, E. Chem. Ber. 1901, 34, 2829.

113. Berti, G. Gazz. Chim. Ital. 1956, 86, 883.

114. a) Ruggli, P.; Meyer, R.E. Helv. Chim. Acta 1922, 5, 28; b) Reissert, A. Chem. Ber. 1913, 46, 1484.

115. Compound was assumed to be trans based on method of formation.

116. The stereochemistry about the ring junction could not be readily determined.

117. Fissekis, J.D.; Markert, B.A. J. Org. Chem. 1966, 31, 2945.

118. Wohl, R.A. Synthesis 1974, 38.

119. McCullough, J.D.; Gould, E.S. J. Am. Chem. Soc. 1949, 71, 674.

120. The NMR spectra from the experiment were compared to NMR spectra of (an) authentic sample(s).

121. Prepared by addition of diazomethane to an ethereal solution of 4-pentenoic acid.

122. Compounds 24' and 25' refer to the carbomethoxy analogues of 24 and 25 respectively.

123. Tarasyants, R.R.; Fedotov, N.S.; Sakovets, O.P.; Luk'yanova, I.A.; Mironov, V.F. J. Gen. Chem. USSR (Engl. Transl.) 1971, 41, 599; Zh. Obshch. Khim. 1971, 41, 603.

124. The integration of the Me_3Si- signal was low due to saturation effects.

125. Dried in vacuo (ca. 0.01 mm Hg) at 100°C for 18 h.

126. Rheinboldt, H.; Giesbrecht, E. Chem. Ber. 1955, 88, 666; see also: reference 31.

127. Prepared by passing anhydrous HCl gas through H_2SO_4 and into dry Et_2O. A saturated solution of Et_2O (100 g) at room temperature contains ca. 33 g of HCl; see; Standen, A.; Ed. "Kirk-Othmer Encyclopedia of Chemical Technology" 2nd Ed.; Vol 11, Interscience Publishers: New York, 1966, p 309.

128. a) Tavs, P. Chem. Ber. 1967, 100, 1571; b) Razumov, A.I.; Moskva, V.V. J. Gen Chem. USSR (Engl. Transl.) 1964, 34, 2612; Zh. Obshch. Khim. 1960, 34, 2589; c) Razumov, A.I.; Savicheva, G.A. J. Gen Chem USSR (Engl. Transl.) 1964, 34, 2617; Zh. Obshch. Khim. 1964, 34, 2595.

129. Reflux condenser was air cooled. Experiment was carried out in fumehood.

130. Resin was freshly activated with 5% (v/v) H_2SO_4 and washed with H_2O prior to use.

131. A 6 ft OV-17, 80-100 W.H.P. Hewlett-Packard prepacked column was used.

132. Clive, D.L.J.; Menchen, S.M. J. Org. Chem. 1979, 44, 4279.

133. Material was distilled using a micro-distillation apparatus. Boiling point quoted is the temperature of the oil bath.

134. Funk, R.L.; Vollhardt, K.P.C. J. Am. Chem. Soc. 1980, 102, 5253; see also: Funk, R.L.; Vollhardt, K.P.C. Synthesis 1980, 118.

135. House, H.O.; Latham, R.A.; Slater, C.D. J. Org. Chem. 1966, 31, 2667.

136. cf. references 134 and 135.

137. The material was dissolved in the minimum volume of the boiling premixed solvent.

138. The ^{13}C-NMR spectrum of the low R_f material showed the presence of ca. 5.5% of another component.

139. Brown, H.C. "Organic Synthesis via Boranes", John Wiley and Sons: New York, 1975; see also: Brown, H.C.; Ravindran, N. J. Am. Chem. Soc. 1972, 94, 2112.

140. The ^{1}H-NMR shows the presence of two isomers.

141. This experiment was performed by Dr. S. Suri.

142. Garbisch Jr., E.W. J. Org. Chem. 1965, 30, 2109.

143. Distilled from anhydrous K_2CO_3.

144. Detty, M.R. Tetrahedron Lett. 1978, 5087.

145. The yield based on recovered starting material (178 mg) was 53%.

146. a) See Table VII for compound 82 ; b) for preparation of thiochloroformate see: Garmaise, D.L.; Uchiyama, A.; McKay, A.F. J. Org. Chem. 1962, 27, 4509.

147. For preparation see: Sharpless, K.B.; Lauer, R.F. J. Am. Chem. Soc. 1973, 95, 2697.

148. Riemschneider, R.; Lorenz, O. Monatsh. Chem. 1953, 84, 518.

149. Marvell, E.N.; Rusay, R. J. Org. Chem. 1977, 42, 3336.

150. The yield of 61c based on recovered starting material was 67%.

151. These are relative peak areas.

152. Evidently isomerization occurred during distillation.

153. Gasanov, A.G.; Mekhtiev, S.D.; Musaev, M.R. Azerb. Khim. Zh. 1975, 6; Chem. Abstr. 1976, 84, 58704h.

154. This material was enriched in one of the isomers (NMR).

155. a) Wharton, P.S. J. Org. Chem. 1961, 26, 4781;
b) Westen, H.H. Helv. Chim. Acta 1964, 47, 575.

156. The spectral data for this compound were not exceptional and the presence of the regiochemical isomer cannot be ruled out.